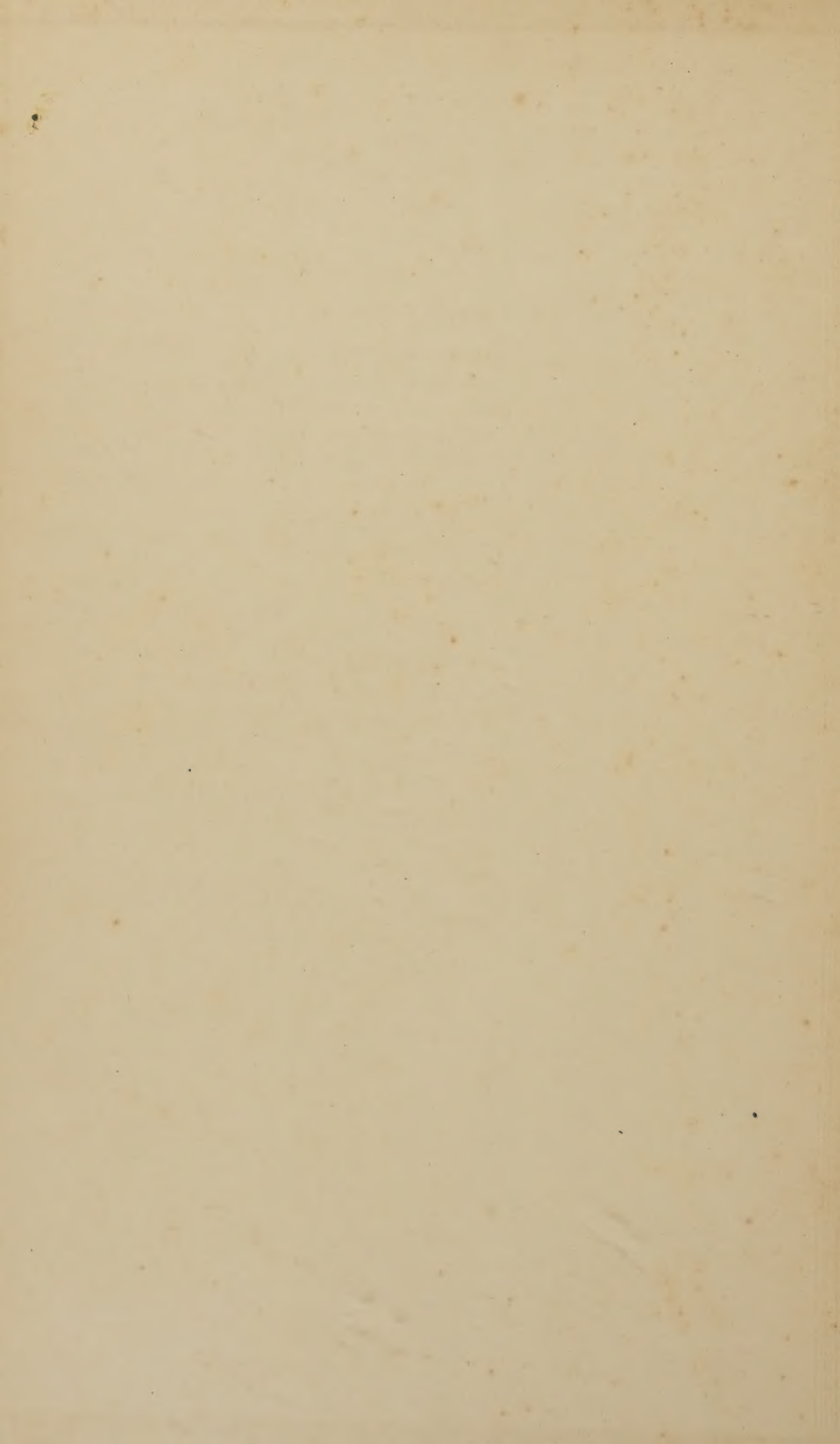






SUPPLEMENT
TO
FORCHHEIMER'S
THERAPEUSIS OF
INTERNAL DISEASES

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PREFACE TO THE THIRD EDITION

Frederick Forchheimer believed that a systematic work on therapeutics was needed by the general practitioner. He was justified by the enormous demand for the first edition. In the preface to the second edition it was stated that the work was a great monument to Forchheimer. With but slight revision of the articles by the contributors, but with an added fifth volume on serum and vaccine therapy, the demand for the second edition was larger than for the first. This manifest popularity of Forchheimer's *Therapeutics of Internal Diseases* justifies the publishers and the editors in the preparation of a new edition.

The continued progress in the knowledge of medicine has brought to light many new facts which modify, more or less, the principles and details of treatment of some important diseases. Every contributor has reviewed and more or less modified his part of the great work and many articles have been entirely rewritten. Some contributors are dead and a few are overseas, engaged in the great world war. The contributions of these authors have been revised by the editors. Dr. Ernest E. Irons has accepted the responsibility of joint editorship with me. The editorial notes made by one or both of us are signed "Editors," to distinguish them from the comments made by Forchheimer.

The work of revision has been a laborious one, but has found compensation in the pleasure and instruction which we have experienced in reading the valuable manuscripts of the contributors.

FRANK BILLINGS.

THE SUPPLEMENT—HOW TO USE IT

This book supplements Forchheimer's "Therapeusis of Internal Diseases" and the second edition of that work which was published under the title of Billings-Forchheimer's "Therapeusis of Internal Diseases."

A new or third edition is now in course of publication and to save our customers who have either of the earlier editions the expense of purchasing this third edition, we have embodied in this volume all new material that will appear in the third edition.

HOW TO USE THE SUPPLEMENT

1. At the top of the page appears a line similar to this:

(B. F.) Pages 609-649 **NUTRITION AND DIETETICS** **Volume I**
(F.) Pages 605-645

The initial (F.) refers to Forchheimer's "Therapeusis of Internal Diseases." The initials (B. F.) to Billings-Forchheimer's "Therapeusis of Internal Diseases." Where no mention is made of either (F.) or (B. F.) it is understood that the page references are identical in both editions.

The page and volume references designate the particular pages to which the new matter refers.

The title of the chapter being discussed appears in the center of the line—in this case, Nutrition and Dietetics.

2. All new material is treated as:

(a) Changes of a few words in text. The new words are indicated by black face type and the line or lines involved are given in full; thus:

199. Lines 29-30 *read*:

The Continuous or Hammock Bath.—The ordinary bathtub is **usually too small** for this purpose.

(b) Additions of one or more sentences or paragraphs; thus:

199. Line 33 *add after* "nates":

If the size of the bathtub be adequate, a hammock bath can be easily improvised at home; (etc.)

THE SUPPLEMENT—HOW TO USE IT

(c) Substitutions of new matter for old; thus:

194. Lines 7-31 *substitute*:

The selection of the remedy has been greatly modified by the addition of Ehrlich's salvarsan to our pharmacal armamentarium; (etc.)

3. In the text of this volume references are again made to (F.) and (B. F.). These references, in conjunction with the page and line numbers, indicate the exact location to which the new material refers in the Forchheimer and Billings-Forchheimer volumes; thus:

21. Line 17 (B. F.) Line 18 (F.) *read*:

chlorid have been unsuccessful. **Hewlett reports malaise and headache after massive doses of urea;** (etc.)

4. The Line referred to is always obtained by counting from the top, disregarding tabular and formular matter.

5. The general Index at the end of this volume covers all references to material in both the Forchheimer and Billings-Forchheimer volumes and also this Supplementary Volume—all clearly indicated by (F.), (B. F.) or (Sup.).

SUPPLEMENT TO FORCHHEIMER'S THERAPEUSIS OF INTERNAL DISEASES

VOLUME I

GENERAL THERAPY

CHAPTER II

ORGANOTHERAPEUTICS

A. JULIUS CARLSON

INTRODUCTION

Definition.—The term organotherapy may be defined as *the successful control of the disease syndrome due to the hypofunctioning of an organ by administration of the organ itself or of substances prepared from this organ*. Other terms, sometimes employed synonymously with organotherapy, are opotherapy, zoötherapy, histotherapy, séquardotherapy, etc.

The above definition strictly excludes *organ transplantation* as a part of organotherapy. It also excludes the principles and methods of using substances derived from animal organs for specific actions not primarily related to the function of that organ in life; for example, the use of pituitrin or extracts of the posterior lobe of the hypophysis to control the uterine contractions in labor.

Organ transplantations has a much wider range of possibilities than organotherapy. When physiology and surgery shall have advanced to a point where an organ like the kidney can be transplanted as a permanent substitute for a diseased kidney, no one doubts that the symptoms of nephritis due to the diseased kidney will be permanently controlled. But no amount of advance of chemistry and biology will ever enable us to cure uremia due to kidney disease by the administration of kidney extracts.

It is, or ought to be, evident that organs like the liver and the kidney, which through the action of their living cells remove toxic substances from the blood, control the chemical equilibrium of the metabolism of the

body not through substances stored up in the cells and given off to the body fluids but through processes dependent upon their living structure. The control of deficiency of this type of organs by administration of organ débris or organ products is as futile as the attempt to repair the effects of a broken wheel in the machinery of a watch by pouring into the watch case a powdered watch wheel. A whole wheel and nothing else will start the watch machinery going. But in actual practice, at present, there is not a sharp distinction between organotherapy and organ transplantation, at least as regards some of the endocrine glands. It is a fact that transplantation of a thyroid or an ovary from one person to another has so far been only a temporary success. The transplanted organ undergoes lysis and absorption, sooner or later; that is, heterotransplantation of any of the ductless glands amounts to little more than the subcutaneous or intramuscular administration of the extracts of these organs. The surgery of heterotransplantation of an endocrine gland is simple, the reasons for only a limited life of the graft are partly known, but there is little hope that the modification of individuality within the species necessary to render the transplant permanent will be an accomplishment of to-morrow.

The continued study of the chemistry and biological reactions of extracts of animal organs will gradually reveal substances having specific and useful drug actions not related to the living rôle of the organ in the intact animal. At present we have two such substances in epinephrin and pituitrin. When epinephrin is used in medicine as a local styptic or in bronchial asthma, and pituitrin to induce uterine contractions, these are as distinctly drug actions as the use of digitalis to stimulate the heart or atropin to dry up the secretions. No one supposes that the physiological actions of the latter alkaloids in the animal body bear any relation to the rôle of these alkaloids in the plants which produce them. The hypophysis antedates the uterus in animal evolution by myriads of ages, and, so far as we know, the mammalian male has the same kind of hypophysis as the female. If the term organotherapy is to include these distinctly drug actions and uses of animal substances, it seems we ought to speak of the useful actions of vegetable alkaloids as *plant organotherapy*.

On the other hand, it is being recognized that some of the effects of well-known drugs are due to specific actions upon organs of internal secretions. Some of the effects of iodine, for example, may be due to the fact that it increases the amount or potency of the internal secretion of the thyroid. There is evidence that certain foods also increase the activity of some organs of internal secretion.

The definition includes the successful use of the digestive enzymes in the control of the disorders of digestion following hypofunction of the digestive glands. But as commonly understood, organotherapy is limited to the organs of internal secretion.

History.—Empirical organotherapy, or the attempt to control symp-

toms of organ disease by feeding the patient the healthy organs of animals, is one of the oldest forms of therapeutics.

The use of animal extracts in medicine is referred to in the "Papyrus Ebers," the oldest manuscript in the history of medicine. Organs or organ extracts of animals had a place in the medical superstitions of the ancient Hindoos and in the therapy of Hippocrates, Dioscorides, and Galen. The naïve empiricism of the organotherapy of the early Greek physicians was not improved upon by the physicians of the Middle Ages. We find that the liver of the pigeon and of the wolf was recommended for hepatic disorders, powdered human heart and the brain of the rabbit for epilepsy, extract of human brain for "debility," the lung of the fox for dyspnea, rennet for gastric disorders, the testicles of the donkey and the stag for depressed sex functions, etc.

It would seem that the use of extracts of lung, liver, kidney, etc., to cure hypofunctioning of these organs presupposes complete ignorance of the physiology of these organs. How much urine will be excreted by a dried and powdered kidney, or how is it possible for a lung extract to send oxygen into and take carbon dioxid out of the blood? But liver, kidney, brain, etc., in powder form, tablets, or solution, are on the market to-day as therapeutic remedies. Studying the lists of organotherapeutic preparations on the market to-day, all claiming support from clinical results (10), one gains the impression that some of our drug manufacturers are guided by the medical superstition of the orient, and by medieval medical lore rather than by the modern sciences of physiology and pathology.

The hundreds of glandular products listed in trade journals, include brain, spinal cord, liver, lung, bronchial gland, lymph glands, spleen, earotid gland, muscle, leukocytes, blood, bone marrow, etc. They do not differ greatly from the lists of a century or two ago; the chief difference is that the "indications" are expressed in more modern but none the less obscure phraseology. The therapeutic use of many of these organ preparations by the physicians of to-day is a discouraging instance of *therapeutic atavism*.

The older organotherapy was based on the belief that it was possible to influence certain diseased organs by the administration of healthy organs; modern organotherapeutics is concerned, primarily, not with the condition of the organ diseased, but with the activities of other organs which are impaired by the absence or diminution of an internal secretion of the diseased organ. Thus thyroid is not given primarily for its effect upon the thyroid gland, but for its effect upon various other organs whose activities are in part dependent upon the internal secretion of the thyroid.

Recent experimental and clinical work in this field has accordingly been directed to two chief aims: (1) the demonstration that various organs produce internal secretions, and (2) attempts to determine the conditions under which these may be utilized for therapeutic purposes.

Great progress has been made in the former attempt; it has been shown that many organs produce internal secretions essential to life, or essential to normal life. Much less progress has been made in the successful utilization of these internal secretions in disease, and we are only beginning to be able to explain the cause of some of the failures.

The first step in rational organotherapy was taken by Brown-Séquard in 1889 in his work on the physiological effects of extracts of the testicles. The work of this French physiologist was not well controlled, and his claims greatly exaggerated. Nevertheless his theory that "all glands, whether they have excretory ducts or not, secrete useful principles, the absence of which is felt when these glands are extirpated, or destroyed by disease," foreshadowed the modern "hormone" physiology. Rational organotherapy was finally established in the early nineties by the successful control of the symptoms of thyroid hypofunctioning by the use of thyroid extract through the work of Schiff, Reverdin, Kocher, Fox, Mackenzie, Murray, and others. This brilliant achievement has had two effects on subsequent biological investigation and clinical practice: (1) It has been a potent stimulus in establishing similar types of function and methods of practical control for other organs of the body; (2) it has stimulated the clinical use of other organ preparations without definite physiological indications of their value and without experimental control.

GENERAL PRINCIPLES OF ORGANOTHERAPY

1. *Successful treatment of the symptoms of hypofunction of an organ by extracts of said organ requires that the essential function of the organ consists in producing a substance or substances in the nature of hormones.*

It follows as a necessary corollary to this principle that organotherapy is out of the question in the case of tissues in which the production and storage of such substances are either absent or of no fundamental importance in the function of the organ. The lung tissue permits or produces the exchange of oxygen and carbon dioxid between the blood and the air. So far as we know the lung tissue does not store any substance that can in any way facilitate lung function or act as a substitute for the living lung. Hence the certain futility of lung extract therapy of pneumonia or pulmonary tuberculosis.

The same general situation exists in regard to the kidneys, the liver, the nervous tissue, the heart and muscular tissue in general, and possibly other organs. No amount of flooding of the body fluid with kidney extracts can separate the urinary constituents from the blood in the absence of living kidney cells. The liver plays a complex rôle in the body, and part of its function may be the production of important hormones, but other important liver functions, such as glycogen storage, protein deamidization, synthesis of urea from ammonia, desaturation of fats,

bile formation, etc., cannot be carried out by any liver extract. The futility of organotherapy in the case of defects or destructive lesions of the nervous tissue is equally apparent.

The only possibility for organotherapy in the case of the tissues just referred to is the chance, or evidence that these tissues contain substances capable of stimulating the impaired organ or organs to increased activity.

For example, the kidney may contain a substance that stimulates the living kidney cells to increased secretory activity although the substance itself cannot secrete urine. It is supposed, for example, that the mammary glands contain lactagogue substances. Substances may be prepared from the gastric mucosa that induce secretion of gastric juice when injected into the blood. The liver contains a cholagogue in so far as it contains bile elements. Nervous tissue is rich in lecithin, and some have held that administration of lecithin is favorable for the growth and metabolism of nervous tissue, etc.

The existence of such specific organotropic substances in these various organs must first be demonstrated by accurate laboratory experiments before one is justified in using such organ extracts on patients, where even under the best of conditions all the factors cannot be controlled. At least one can place no credence on the results of such clinical use of organ extracts until supported by laboratory experiments on animals. This principle must be insisted on all the more since many of the clinical lesions of the kidneys, lungs, liver, and brain can be reproduced experimentally in animals.

A typical case in point is the testicular "spermin" of Poehl, which was proclaimed as a general metabolic stimulant and for a time used as a "cure-all" by a few uncritical enthusiasts.

2. There is little or no hope for successful organotherapy in diseases due or supposed to be due to a primary hyperfunction of organs.

Where a malady is definitely traced to primary hyperfunction of an organ the remedy is surgical (direct or indirect), not medical. But the question of an out-and-out organ hyperfunction inducing serious clinical disorders is at present a complex and uncertain chapter in medicine. Gastric hypersecretion or hyperacidity is supposed to cause certain symptoms in gastric and duodenal ulcers, and in so-called vagotonia. The syndromes of toxic goiter, acromegaly, hemolytic jaundice, and certain types of anemia, hypergenitalism, and osteomalacia are held by many scientists and clinicians to be caused by hyperactivity of the thyroid, hypophysis, spleen, pineal body, and gonads respectively. If it shall be clearly established that sufficient hyperactivity of these and other ductless glands cause disease, the only type of organotherapy that may be of value is the administration of organ extracts that depress the hyperactive gland—if there are such extracts. For example, it has been recently reported that administration of ovarian extract to young males retards

the development of the testes, and the observations of Lillie on the Free Martin seem to show that the testicular and ovarian secretions have some mutual inhibitory action on the development of the respective sex characters. This type of organotherapy is, at present, purely empirical and should be well grounded by animal experiments before it is applied to patients. If the hyperactivity of the gland is a compensatory one, administration of extract of that gland might arrest the gland growth but would not control any other symptoms. If the glandular hyperplasia and hyperactivity is primary such organotherapy is clearly contraindicated.

3. *There are at present no definite indications for organotherapy in diseases due or rather supposed to be due to organ dystrophy, that is, a perverted or pathogenic secretion.*

The theory of a perverted or pathogenic secretion as the cause of disease has been advanced for some of the maladies related to the ductless glands, notably the thyroid and hypophysis. The theory has little or no basis in fact. But assuming it is true, the following possibilities must be considered: (1) The gland may yield both the normal and the pathogenic secretion. In that case the patient will show no symptoms of glandular hypoactivity, the symptoms of the disease being solely due to the perverted secretion. In such a case specific organotherapy would in all probability prove useless, as there is no reason for believing that the normal secretion of the gland would control the pathological secretion. (2) In yielding the pathological secretion the gland may be so altered that the normal secretion is diminished or absent. This is the most likely condition. In such a case the syndrome would be a complex of glandular hypoactivity and pathogenic secretion, and it is obvious that organotherapy might have a favorable effect on the hypoglandular symptoms but leave the pathogenic secretion symptoms unaffected.

4. *The hormone or hormones must be stored up in active form and in some quantity in the organ producing them, for successful organotherapy of this organ.*

It is obvious that unless the specific hormone in question is stored in the gland to some extent, administration of the gland extract in hypofunction of the gland will be useless. For example, a glycerin extract of gastric mucosa contains pepsin, but no hydrochloric acid, although both of these substances are produced by the gland cells and are of equal importance in gastric function. The reason is evident. Pepsin is stored up as pepsinogen in the resting cells while the hydrochloric acid is not stored up but discharged from the cell as soon as formed. Hence a gastric mucosa extract contains the former but not the latter, and in organotherapy of the gastric mucosa hydrochloric acid must be added from some other source. Analogous conditions may obtain in some of the endocrine glands. It is therefore important to determine to what extent the internal secretions are stored in the organs producing them, and how much

of it is necessary to maintain health. This is possible, in a general way, in the case of a few organs. Thus, from studies on the amount of thyroid which it is necessary to administer to maintain health in animals or man suffering from removal or disease of the thyroid, it is possible to form an approximate estimate of how much thyroid secretion is necessary, and from the weight of the gland how much material is stored in it. Such calculations show that the thyroid contains sufficient secretion to meet the demands of the body for several weeks.

From a determination of the amount of epinephrin (one of the internal secretions of the suprarenals) contained in the blood of the suprarenal vein, and from the rate of blood flow through the suprarenal glands, it is possible to make a rough estimate of the amount of epinephrin produced (and possibly needed) daily. When this amount is compared with that actually found on chemical analyses in the suprarenal glands, it is found that the latter is not sufficient to meet the needs of the body for more than a few hours. Since some of the internal secretion is almost invariably lost or destroyed in the manipulations necessary to prepare the gland for administration, it is evident that the conditions in the case of the thyroid are far more favorable for success than in the case of the suprarenals. (Other reasons for expecting far more success from thyroid than from the epinephrin will be discussed later.)

Although there is little doubt that the pancreas and, possibly, the parathyroids form internal secretions essential to life, attempts to demonstrate their presence in the glands have so far failed. Either the secretion passes into the blood as rapidly as it is formed, or, if some of it is retained in the gland it is destroyed by the physical and chemical manipulations necessary for the removal of other cell constituents.

In addition to knowing how much of the secretion is stored in the gland, it is important to know how urgent is the body's need for the secretion, and how long the latter remains in the body. Light on these questions has been obtained by determining how soon symptoms appear after the removal of the glands. Taking two extremes, it has been found that symptoms may not appear for weeks or months after removal of the thyroid, whereas they appear within four to eight hours after removal of the pancreas. It is evident that the chances for successful organotherapy are much more favorable in the former case.

5. The physiologically important hormone stored in the gland must be sufficiently stable to resist the necessary chemical and physical processes of making the gland extract; and, for practical organotherapy, the hormone must resist the action of the digestive enzymes, and must be absorbed into the blood in active form.

This is probably the most serious limitation of organotherapy. All hormones are probably soluble in serum or Ringer's solution. But because of the necessity of continuous or daily administration, intravenous or

hypodermic injections of extracts of the entire glands produce toxic effects, in some cases more serious than the symptoms treated, owing to the presence of injurious tissue split products. The chemical manipulation necessary to remove these toxic by-products introduces greater chances for decomposition of the hormones themselves. Moreover, intravenous or hypodermic injections must be done by a physician or a nurse, and even when this is done there are chances for local and general infections when employed daily or several times a day for months and years. *Practical organotherapy thus limits itself in most cases to administration of the gland or the gland extract by mouth.* That is, the hormone must run the gamut of enzyme action both in the lumen of the alimentary tract and in the wall of the absorbing intestine. In view of this fact, the failures of organotherapy are less surprising to biologists than the single success in the case of the thyroid. If the founders of thyroid organotherapy had known of the general completeness of the protein and fat hydrolysis in the digestive tract we believe they would scarcely have had courage to try the feeding of thyroid in myxedema and cretinism.

Classical examples of destructive action of the digestive enzymes on physiologically important hormones, or failure of these hormones to reach the blood in active form when administered by mouth, are the *epinephrin*, and the *pancreatic* and *gastric secretins*.

6. *The hormone must be present in the gland in active form; be activated by the chemical processes of preparing the extract; or the normal activator added to the gland or the extract.*

The thyroid hormone and epinephrin are present in the gland in active forms or activated by the processes of extraction. Whether any of the other internal secretions are stored as pro-hormones and must be activated in or by the products of other organs has not yet been determined. Münzer assumes that all the endocrine glands work in pairs, one activating or inhibiting the other. He therefore concludes that before an organ is used in organotherapy it must be "activated" by previously removing the inhibiting gland from the animal. For example, before using the pancreas of an animal to control pancreatic diabetes in a patient, the animal must have had the anterior lobe of the hypophysis extirpated some time before the pancreas is excised in order to yield an "activated" pancreas. This fanciful theory is not borne out by the well established facts of thyroid organotherapy, and we shall point out later that extirpation of some of the alleged inhibitors of the adrenals do not influence the epinephrin content of the gland.

Hédon claims that, when the blood from the pancreatic vein is introduced into the portal circulation of a diabetic animal, there is a diminution of the glycosuria, while it has no effect when introduced into the general circulation. Thus, he concludes that it is necessary for the internal secretion of the pancreas to reach the liver in order that it may be active.

But Hédon's results are disputed by Carlson. In any event, it is a fact that the establishment of an Eck fistula in animals does not induce hyperglycemia and glycosuria on ordinary carbohydrate rations, despite the fact that by this operation all the portal blood, including that from the pancreas, is sent into the general circulation before a small fraction of it reaches the liver by way of the hepatic artery. Hédon's theory is untenable in view of this fact. But we have a classical example of such "distant activation" in trypsinogen and enterokinase; and the possibility of analogous conditions in the ductless gland where all attempts to isolate or demonstrate active hormones have so far been failures must always be kept in mind and tested.

7. *The hormones must be relatively stable in the form in which the gland or gland extract is put on the market for therapeutic or research purposes; and the organ preparations must, so far as possible, be chemically and physiologically standardized.*

No argument is needed in defense of this principle, although it is not always complied with. Stability of the hormones may not be attainable, in which case we must have recourse to fresh glands or fresh extracts. The only criticism that may be legitimately directed against manufacturing concerns in such cases is for failure to indicate the date of preparation of and the rate of deterioration of the extract. While pancreatic secretin has so far proved to be of no therapeutic value, it can be prepared in active form, but not kept from rapid deterioration, so that the preparations on the market become inert in a few weeks. This would be serious in case the active secretin was of any value in curing or controlling disease.

The chemical and physiological standardization of such substances as thyroid, pituitary, and adrenal extracts is just as important as the standardization of diphtheria antitoxin. It should be insisted on by the profession, and required by law, in view of the fact that the preparations on the market show such great variations in physiological activity. This is obviously a great drawback to the successful use of these substances in disease.

The importance of chemical and physiological standardization of preparations of the parathyroid and the corpus luteum is equally obvious. The parathyroids are very small organs, distributed on *and in* the thyroids and, in some cases, in the thymus. It takes a good deal of training and care to avoid the inclusion of small accessory thyroids, or nodules of thymus in gathering fresh parathyroid material. There is some evidence of variation in function of the corpus luteum with the age of this temporary organ, and with the incidence of pregnancy. Even the most careful manufacturer therefore is facing great difficulties, since his only sources of material are the abattoirs and the only criterion of the time of ovulation in the abattoir animals is the appearance of the ovary by direct inspection.

Dannereuther states that only one of the several drug firms who place

ovarian products on the market would affirm that their corpus luteum preparations are made from the corpus luteum of pregnant animals.

8. *In case of the endocrine glands in which organotherapy is still in the balance the clinical use of organ extracts should be most rigidly controlled and should be preceded or paralleled by animal experiments.*

Empirical organotherapy is not to be condemned entirely, but when organ extracts are used in this way without the guidance or positive indications from physiology and pathology, medical progress demands that other factors be eliminated so far as possible, so that the results may have some meaning. A careful perusal of the literature will convince any candid man that we are great sinners in this regard. Our age has been characterized medically as one of therapeutic nihilism. On the contrary, in the field of ductless glandular diseases and organotherapy, it is an age of therapeutic credulity and foolish faith in the biological and medical omniscience of drug manufacturers.

The ideal scientific control is not easily attained in most clinical cases. There are the spontaneous fluctuations in the severity of symptoms, spontaneous repair irrespective of all therapy, and factors of general hygiene and nutrition which the good physician always endeavors to improve. There are the uncertainties of diagnosis, especially in the so-called pluriglandular diseases. Hence the value of the guide and aid of definitely controlled animal experiments. Clinical results will ever constitute the final test of organotherapy in any given condition, but intelligent co-operation of the clinic and the laboratory will assure a quicker arrival at the truth.

A complete organotherapy is probably not attainable. In the normal animal hormone equilibrium is balanced by delicate chemical and nervous processes. When this equilibrium is upset by disease, it is probably impossible to restore complete balance by our relatively crude methods of organ extract administration. It must not be forgotten, however, that we are aided by the wonderful plasticity and capacity for readjustment on the part of the organism, at least under many conditions.

Classification.—At present the only practical method of classifying organotherapeutic products is by the organs from which they are derived. Such a classification, however, is already too narrow, and, with the further growth of knowledge, may have to be abandoned altogether. One or two illustrations will suffice: Among the symptoms of suprarenal insufficiency are low blood pressure and an enfeebled heart, due directly or indirectly to loss of the gland. The arterial hypotonus may be controlled temporarily by the administration of suprarenal extract. But epinephrin is equally effective in conditions of arterial hypotonus occurring independently of the suprarenal glands. The same is true of an entire system, viz., practically all the organs innervated by the sympathetic nervous system. This particular secretion of the suprarenal (epinephrin) may

be classed as a "sympathomimetic" (Barger and Dale) drug, i. e., a drug the action of which is similar to that of sympathetic nerves. The use of extracts of the posterior lobe of the hypophysis in obstetrical practice belongs to the same category. Thus, they pass from the present classification altogether. As knowledge advances, this will probably be the case with most of the substances now treated under the head of organotherapeutics.

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THYROID

The employment of thyroid in medicine in cases of congenital absence, atrophy, or destructive lesions in the gland in patients is a typical case of substitution therapy. It is also in reality *our only established case of successful organotherapy*. The marked result with this organ has been the main impetus and guide in the attempts to work out an organotherapy for the other endocrine glands. The thyroid produces a substance or substances of specific physiological importance, stable *in vitro*, not destroyed by the digestive juices or the bacteria of the alimentary canal, and absorbed in active form into the blood. The functions of the gland may be partly replaced by the administration of the gland. So well established is this principle that conditions of the thyroid can be diagnosed from the effects on the body of the administration of the gland.

The administration of the thyroid in organotherapeutics is based partly upon clinical and partly upon experimental work. The latter preceded the former,* but the two methods have been closely combined, each reacting upon the other. The gland was not employed in medicine until a rational basis for its use had been established experimentally; empiricism had no part in its introduction.

The basis for its use will be made most clear by a brief review of the

* The first attempts to combat thyroid deficiency were the transplantation experiments in dogs by the physiologist Schiff; these were the direct stimuli to similar experiments in man.

physiology and the pathology of the gland. We are not concerned with the various hypotheses of thyroid function that prevailed in medicine up to the work of Schiff, Riverdin, and of Kocher, beginning 1856. It is true that previous to this work thyroidectomy had been made in animals, mostly for therapeutic purposes (goiter) but with varying results. The only valuable early observation appears to be that of J. F. Merkel that there is ordinarily an increase in the size of the thyroid in women during menstruation and during pregnancy, thus showing a close relationship between this gland and the sexual cycles of the female.

The most important steps in our knowledge of the thyroids are the following: (1) the demonstration (by Schiff, Riverdin, Kocher, and others) that extirpation of the thyroid in adults leads to a series of disturbances designated by the term *cachexia strumipriva*, or myxedema; (2) the experimental production of cretins by removing the thyroid in young animals, and the recognition of sporadic and endemic cretinism in man as due to hypothyroidism; (3) the demonstration that the symptoms of hypothyroidism can be partly controlled by thyroid administration (Ewald, Baumann, Magnus-Levy, Pick and Pericles, Murray, Howitz, Mackenzie, Fox, Kocher, and others); (4) the discovery of the thyro-iodin, and the subsequent studies of specific thyroid chemistry (Baumann, Oswald, Hunt, Marine, Koch, Kendall); (5) the demonstration of a definite relation of thyroid physiology to the diet (Watson, Hunt, Marine, Bensley) and possibly to infectious processes (McCarrison, Rosenow); (6) the studies of the possible control of thyroid activity through secretory nerves and circulatory changes (Asher, Watts, Cannon, and others).

From the standpoint of clinical medicine one of the most important problems in thyroid physiology remains yet unsolved, namely, the cause and significance of the thyroid changes in so-called toxic goiter in man.

FUNCTION OF THE THYROID GLANDS

The thyroid develops from the epithelium of the bronchial clefts of the embryo. The embryological anlage of the thyroid is thus similar to that of the parathyroids and the thymus gland. In the adult normal animal the thyroid is made up of acini of cuboidal cells with the thyroid colloid filling the center of the lumen. In mammals this adult structure begins to appear at or a little before birth. In earlier intra-uterine life there is no colloid or definite arrangement of the cells into acini.

The colloid is obviously a cell product (cell degeneration or cell secretion). But its relation to the gland function is not yet clear. Bensley has recently succeeded in staining an intracellular thyroid colloid. This colloid is most abundant in the region of the cells adjacent to the lymph and blood vessels. It is usually held that the colloid in the lumen of the acini represents a storage state of the physiologically important internal

secretion, which, according to the needs of the body, becomes changed, is reabsorbed by the cells, and passed into the blood stream.

The blood and lymphatic supply to the thyroid is very abundant, so that the blood flow through the gland per mass of tissue is greater than in any other organ in the body. Manley and Marine have recently shown that a piece of the thyroid transplanted to other regions of the body stimulates the development of a similar extraordinary blood supply. The great vascularity of the thyroid is therefore intimately related to its specific function.

The Significance of the Thyroid Innervation.—Branches from the cervical sympathetic nerves pass along the thyroid vessels to the gland. These thyroid nerves have with certainty a vasomotor function. Their stimulation causes primary vasoconstriction in the gland, and this is followed by vasodilatation at the end of the stimulation.

The question whether there are also true secretory fibers in the thyroid nerves has been attacked by diverse methods without as yet yielding conclusive results. Asher and Flack, also Ossakin, report that stimulation of the thyroid nerves increases the excitability of the depressor reflex mechanism, due to an increased thyroid secretion thrown into the blood. Rabe, *et al.*, found that the stimulation of the nerves reduces the iodine content of the gland, and this was confirmed by Watts, but the latter investigator also found that identical decreases in iodine were induced by mechanically produced circulatory changes (temporary vasoconstriction) in the gland. Cannon reports that a successful union of the phrenic nerve with the cervical sympathetic induces some of the symptoms (nervousness, exophthalmos, increased metabolism) of thyroid hypersecretion, owing to the continuous respiratory nervous discharges from the phrenic acting on the gland cells. The fact itself is contradicted by Troell, but if it shall be proven correct, as reported by Cannon, the excessive thyroid activity may be due to circulatory rather than secretory nerve disturbances. Cannon also finds that stimulation of the thyroid nerves produces an electrical change in the thyroid similar to that induced in muscle or in nerve when thrown into activity. This he interprets as proving a direct secretory nerve action. However, Schäfer has reported similar electrical changes in the mammary gland on injection of pituitrin, and it is now demonstrated that pituitrin causes, not milk secretion, but merely a discharge of the milk present in the duct system by contraction of the duct musculature. Moreover, the electrical response in the thyroid, as reported by Cannon, was sometimes positive and sometimes negative. It does not seem possible at present to interpret both of these effects as due to an increased secretory activity. Moreover, denervation of the thyroid in normal animals does not produce hypothyroidism, and transplanted fragments of thyroid appear to function in a normal manner without nerves.

If secretory nerves are present they are certainly not necessary for the

normal gland function. The control of the gland activity is therefore essentially a humoral one, as indicated by the great vascularity. But the question of thyroid secretory nerves is nevertheless one of great practical importance in relation to the cause and control of possible hyperthyroidism.

CHEMISTRY OF THYROID

The older investigators reported the presence in thyroid of albumins, nucleoproteins, albumoses, leucin, xanthin, hypoxanthin, lactic and succinic acids, etc. In glands which have undergone cystic degeneration the finding of mucin, cholesterolin, methemoglobin, bile pigments, etc., is reported.

Since the discovery in 1895, by Baumann, of iodin in the thyroid, interest in the chemistry of the gland has centered largely around this element, and the substances with which it is in combination.

The amount of iodin in the thyroid, not only of man, but of the lower animals, is extremely variable, being influenced by age, character of the food, locality, the physiological conditions of the thyroid, and many other, for the most part unknown, factors. The thyroids of infants and of newly born animals contain less iodin than adult thyroids; in fact, it cannot be detected at all in many cases, at least not by the use of usual quantities of the gland, and by the usual methods. But the same is true in many instances of the thyroid of adults and to all appearance normal animals. Aschbacher gives the average amount of iodin in the human thyroid between the ages of twenty-five and thirty as 8.98 milligrams; it is less both in youth and old age. The percentage based on the weight of the dry gland varies from zero to 0.4 or 0.5. Extreme variations both in the total amount and in the percentage occur. The thyroids of salt water fish contain three times the amount of iodin usually present in the mammalian thyroids. In some of the marine invertebrates iodin is present in great quantities in some of the cutaneous and excretory structures where the iodin cannot have the physiological significance it has in the thyroid of the vertebrates.

The nature of the iodin complex in the thyroid is unknown, notwithstanding the large amount of work which has been devoted to the problem. The form is specific for the thyroid; no other iodin compound is known which has the specific physiological properties of the thyroid substance (v. Fürth, Schwartz, Koch, MacLean, Hunt and Seidell). It is known to be united in some way to the proteins, probably to one or more of the amino-acid constituents of these (Koch, Kendall, Cameron).

Baumann isolated a specific but ill-defined iodin compound from the thyroid, one which has at least many of the specific properties of the gland substance itself. He named this substance iodothyryn.

Oswald isolated, at least approximately, the protein with which the

iodin is combined. He named this protein thyroglobulin; it was found to constitute one-third to one-half or more of the weight of the dry gland. The iodin content varied from zero to 0.86 per cent. or more. Oswald believed this thyroglobulin, when it contained iodin, to represent the true active principle of the thyroid; Baumann's iodothyrim could be obtained from it by hydrolysis.

Oswald also isolated an iodin-free protein having the properties of a nucleoprotein, but this protein did not have the characteristic physiological thyroid action.

F. C. Koch found that as determined by the acidonitril test of Hunt, the thyroglobulin as well as the metaprotein fraction of the thyroid retained the full physiological activity of the entire thyroid. Further hydrolysis into iodothyrim, and primary or secondary albumoses show a gradual decreasing activity, while the amino-acid fractions show little or no physiological activity, although they retain some of the iodin. The thyrometaprotein of Koch contains three times the percentage of iodin found in the entire thyroid, yet it shows no greater physiological activity than the dried thyroid. The relation of the iodin to the physiological activity of the thyroid thus appears not to be a direct one.

Kendall reports the separation of the physiologically important thyroid constituents by alcohol precipitation into two fractions: (1) a smaller one, *A* or alpha fraction, insoluble in alcohol and containing ten times the percentage of iodin of the original thyroid—this alpha fraction is toxic, and its administration produces the typical symptoms of excess thyroid feeding; (2) the alcohol soluble fraction, *B*, contains less iodin and is not toxic, but its administration is said to improve many of the conditions of myxedema in man, particularly the skin conditions. This could not be confirmed by Basinger on cretin rabbits. The *B* fraction (material prepared by Kendall) was less toxic to cretins than commercial thyroid preparations, but it had no effect on skin conditions or on the growth. Basinger found, however, that the thyroid metaprotein of Koch had the same good effects on rabbit cretins as the original thyroid.

Relation of the Iodin to the Physiological Activity of Thyroid.—

Baumann's discovery of iodin in the thyroid stimulated an immense amount of work, and led to the accumulation of a large number of facts as to the occurrence of iodin in the thyroids of various animals, and in those of man, under various conditions, both pathological and normal. The fact that iodin can frequently not be detected in the thyroids of healthy individuals has led many to doubt whether this element is a necessary or important constituent of the gland (*cf.* Hunt and Seidell, Carlson and Woelfel). From almost the beginning there has been evidence, not very conclusive, however, that the activity of the thyroid when used as a drug is closely dependent upon its iodin content. Thus, Roos in three experiments upon dogs found that more nitrogen was excreted after

the administration of thyroid rich in iodine than after that of thyroid containing little iodine. Roos also administered thyroid containing different amounts of iodine to four patients with parenchymatous goiter; that containing the largest amount of iodine was the most active in diminishing the size of the goiter. Oswald also found in two experiments thyroglobulin rich in iodine to cause a greater excretion of nitrogen than did thyroglobulin poor in iodine. Marine and Williams found in two experiments that thyroid containing a larger percentage of iodine caused a greater loss of weight in dogs than did a preparation containing a smaller percentage.

Hunt, and Hunt and Seidell, in extended series of experiments, in which the effect of thyroid upon the resistance of animals to certain poisons was determined, found a close parallelism between the physiological activity of the thyroid and its iodine content. They also found that the iodine which accumulates in the thyroid after feeding iodine compounds is present in an active form, that is, in the form characteristic for the thyroid. In the same species large thyroids (goiter) contain a smaller percentage of iodine than small thyroids, and correspondingly pressure juice from large thyroids exhibits less physiological activity than that from small thyroids.

Although further clinical tests are desirable, the above experiments offer almost conclusive evidence that the therapeutic value of thyroid is directly proportional to the iodine content (Koehler). It is well established that feeding iodine in any form leads to a rapid increase in iodine in the thyroid, but it is not known whether the iodine thus stored is immediately incorporated as the physiologically active thyro-iodine compound. Possibly the thyroids may store iodine outside of this compound, for example, in the colloid.

Several writers have called attention to the variation in the iodine content of commercial thyroid preparations; Hunt and Seidell found the preparations on the American market to vary from 0.095 to 0.38 per cent. The average was approximately 0.2 per cent.

It is thus evident that the commercial preparations vary by as much as four hundred per cent. Such variations in the strength of most drugs would be considered intolerable, and there can be little doubt that more satisfactory results would often be obtained if the thyroid preparations were more uniform in strength. That lack of uniformity does not cause more inconvenience is due largely to the fact that thyroid medication must, by its nature, be peculiarly individual; the dose must be governed by the degree of thyroid deficiency of the patient, and this can only be determined by trials with different doses. When, however, the proper dosage of a certain preparation in an individual case has been determined, it would be distinctly advantageous to be able to continue the same dosage if a fresh supply were prescribed; at present, even if the same firm's preparation

were prescribed, the second order might be several times as active as the first. Hence, it would be very desirable for the pharmacopeia to fix a standard iodine content for the official preparation; a standard of 0.2 per cent. would seem reasonable (Hunt and Seidell). This iodine content must, of course, represent the physiologically active thyroid substance, and not the addition of other organic or inorganic iodine. For that reason the chemical standardization by means of the iodine percentage should be supplemented or controlled by physiological standardization (the acetonitril method of Hunt, or the cretin method of Basinger).

The Relation of Thyroid to Diet.—It has been shown by Watson (on the rat), Marine and Lenhart, and Gaylord and Marsh (for the salmonoid fishes), and Bensley (for the opossum) that a high or otherwise abnormal protein diet induces thyroid hyperplasia and marked enlargement of the gland. In the case of the brook trout this hyperplasia followed feeding with mammalian liver or uncooked animal protein, and was promptly stopped by feeding with fish or cooked meat. McCarrison was able to induce thyroid hyperplasia in rats by feeding extract of feces from goiter patients. But we are not permitted to generalize from these observations, although they are both interesting and important, for high protein diet, or feces from goiter (toxic) patients fails to induce these thyroid changes in other species (cat). Evidently the thyroid stability or factors of safety varies greatly in different species.

Feeding meat is said to reduce the iodine content of the thyroid. This may be a factor in the hyperplasia.

Hunt found that mice fed on oatmeal or on oatmeal and liver showed a much greater resistance to acetonitril than mice of the same litter fed on eggs, crackers, and milk. He ascribes this difference to a greater stimulating action of the oatmeal and the liver diets on the thyroid gland.

Prolonged starvation leads to degeneration and atrophic changes in the thyroid (Jackson).

Secretion versus Detoxication.—Bensley and others claim to have identified the thyroid secretion in the cells by microchemical methods much in the same way as the secretion granules or pro-secretion of the digestive glands have been brought out by staining. But the presence of the secretion as a normal element in the body fluids has not been demonstrated. Our strongest evidence that the thyroid works by the mechanism of an internal secretion rather than by processes of detoxication is the result of thyroid organotherapy in experimental and clinical hypothyroidism. Those results are capable of no other interpretation. But this does not exclude detoxication processes in the thyroid; in fact v. Cyon's theory is partly true. Because of the special affinity of the thyroid for iodine, iodine compounds of all kinds—including the more or less toxic inorganic iodides—are taken out of the body fluids and turned into the less toxic thyroglobulin. But this work can be performed by the kidneys as

an elimination process, and at any event it is of secondary importance in thyroid physiology, for the entire thyroid function can practically be taken by the dried and dead thyroid product.

The Thyroid Secretion and the Body Fluids.—Probable as it seems from experimental and clinical data that the normal thyroid yields a secretion to the body fluids, yet it must be admitted that this secretion has not yet been demonstrated in the blood or the lymph, even in the lymph taken directly from the thyroid gland. The colloid observed, by histological method, in the thyroid lymphatics is probably an artefact. The acetone-nitril test on normal blood of men and animals is negative (Hunt, Carlson and Lussky). Even in the cases of blood from exophthalmic goiter patients the method yields inconclusive results. Trendelenburg reports that the blood of thyroidectomized cats yields a positive acetone-nitril test—a fact which seems to call in question the validity of the test itself.

Basinger transfused repeatedly blood of normal rabbits into cretin rabbits without observing any effects on the cretin conditions; but when similar transfusions were made into the cretins of blood from rabbits fed varying quantities of commercial thyroid, the cretin condition was influenced in the same manner as by feeding thyroid.

It is altogether probable that the thyroid secretion is present in normal blood, but in too small concentrations for detection. This is indicated by some work of Doctors Woelfel and Luckhardt, not yet published. These investigators find that when the blood from dogs with high iodine content of thyroid is transfused into dogs (previously bled dry) with low iodine content, the percentage of iodine in the thyroid of the latter is increased. This seems to show that there is a balance or equilibrium between the stored thyroid secretion in the gland and the circulating thyroid secretion in the blood. This gives us hope that the question of thyroid secretion in the various types of thyroid hyperplasia may yet be solved by blood analysis. Cannon reports that epinephrin stimulates the thyroid gland to greater activity.

The Relation of the Iodine to the Histological Structure of the Thyroid.—If iodine is a necessary constituent for normal thyroid function it would seem that it would be equally necessary for normal thyroid structure. Nevertheless, in exceptional cases in most animals and, as a rule, in some species, iodine in structurally normal thyroids is either absent or so small in amounts that it cannot be demonstrated by our best chemical tests. The most significant findings in the relation of the iodine to thyroid structure are the observations of Marine, Bensley and others, namely, that most types of thyroid hyperplasia can be arrested and converted into a colloid or resting state by the administration of iodides in any form. We are not permitted to conclude from this fact that the hyperplasia which is controlled in this way is due to lack of iodine in the food or in the body. This arrest of the hyperplasia may be a drug action of the iodine, or an

evidence of a detoxicating rôle of the thyroid, as suggested by v. Cyon, the excess of inorganic or toxic iodine being converted by the thyroid into a non-toxic or a less toxic form. According to Bensley, the thyroid hyperplasia induced in the opossum by excessive protein diet is not arrested by iodids.

According to Jones, and Jones and Tatum, increasing the iodine content of the thyroid increases the stainability of the thyroid colloid, so that the amount of iodine in the gland can be in part determined by reaction of the colloid to Mallory's connective tissue stain.

The specific affinity of thyroid tissue for iodine is retained in certain stages of malignant growths of the thyroid, primary and secondary. The fact that the iodine complex in these thyroid tumors represents active thyroglobulin has not yet been established.

Sweet and Ellis report that removal of the external function (pancreatic digestion) of the pancreas leads to an increase of iodine and colloid in the thyroid glands.

According to O. Ewald the colloid found in the thyroid lymphatics, at times, is not a true thyroid secretion, but a decomposition product, not utilizable by the organism.

THE RELATION OF THYROID HYPERPLASIA TO THYROID NEOPLASM

Thyroid hyperplasia predisposes to thyroid neoplasm. In dogs malignant growths of the thyroids with typical bone, lung, and liver metastases are not infrequently found on the basis of an old goiter. We have never seen it start from a normal thyroid.

The line of demarcation between simple hyperplasia and malignancy would seem to be metastatic growth. Yet something like metastatic spreading growths appears to be a normal phenomenon in the thyroid of fishes, where the glands are not surrounded by a connective tissue capsule (Gudernatsch). This has led to contradictions and confusions in the interpretations of the thyroid hyperplasia or thyroid cancer so common in salmonoid fishes, especially under domestication.

Marine and Lenhart regard these thyroid growths as simple hyperplasia, since they respond to the same measures that modify simple thyroid hyperplasias in mammals. Gaylord and Marsh, on the other hand, regard all stages of this hyperplasia as malignant neoplasm. This appears to the writer as an extreme position. If this view is tenable for fish, it should be equally tenable for mammals, in which case thyroid hyperplasia in man and other mammals becomes a cancer problem. Gudernatsch has pointed out that the metastases of normal fish thyroids do not cause destruction of adjacent tissue. The same is certainly true for simple thyroid hyperplasia in the higher animals. At the same time malignancy in the primary thyroid tumor is probably present some time before metastatic growth

occurs, so that a sharp line between simple hyperplasia and malignancy of thyroid growths cannot be drawn.

HYPERTHYROIDISM, EXPERIMENTAL AND CLINICAL—TOXIC GOITER

The effects of hypothyroidism, experimental and clinical, are clear; and their control is partly in our hands through organotherapy. This cannot be said of the causes and effects of hyperthyroidism—if, indeed, there is such a thing as continued hyperactivity of the thyroid with attendant symptoms of disease. Hyperplasia of the thyroid gland occurs in man and animals under many conditions. We have seen that in some animals it may be experimentally induced by the diet. In women there occurs what may be called a strictly physiological hyperplasia at puberty, at menstruation, and during pregnancy, although some of the enlargement of the thyroids at these periods may be simply due to increased vascularity. The period of active growth of simple or benign goiter is really a period of hyperplasia. According to Marine a colloid goiter represents a relatively resting stage of a previous hyperplasia. Finally, in so-called toxic goiter, or Basedow's disease, there is usually proliferation of the thyroid cells, increase in gland volume and gland vascularity, with decrease in gland colloid. As a general rule the amount of colloid in the thyroid is inversely proportional to the rate of cell division and growth of the gland at any period.

The mere facts of the anatomical changes in the gland are well established; the causes and consequences of these changes are in dispute. Wilson and Kendall found that the alpha or toxic iodine compound of Kendall is present in hyperplastic glands of toxic goiter only in amounts of one-tenth to one-fifteenth found in normal glands; they conclude that this is due to increased secretion or absorption into the blood, and that it is this toxic iodine compound which is responsible for the symptoms of toxic goiter.

Lampe claims that there is an increase in specific thyrolyns in the blood in toxic goiter, myxedema, as well as in endemic goiter. In Basedow the serum also digests thymus and gonad tissue.

In moderately severe cases of Graves' disease Geyelin reports that 70 per cent. of his cases showed a lowered sugar tolerance. Milder cases have normal blood sugar. Feeding thyroid to myxedematous patients may induce hyperglycemia.

It must be noted, in the first place, that mere increase in cells and gland volume does not mean increased activity or increase in the secretion. A mere fraction of the normal thyroid suffices to meet the normal needs of the organism. This means that the thyroid under normal conditions does not work up to full capacity; hence it should be possible to greatly increase the rate of thyroid secretion without increase in the number of cells. If,

as seems probable, the thyroid activity is governed mainly by the blood, doubling the thyroid volume would no more increase the thyroid secretion than doubling the kidney volume would increase the quantity of urine. The reverse experiment has not been made, but we predict that when made, that is, when two healthy kidneys are successfully implanted, say on the carotids in the neck, the sum total of urine secreted by the four kidneys will be no greater than that secreted by animals' own kidneys before the implantation.

In the second place, gland cells in condition of active division and proliferation are probably not sufficiently differentiated to perform a highly specialized function. And in the third place, we have as yet no reliable test, histological, physiological, or clinical, for the rate of thyroid activity at least covering longer periods than ordinary crucial experiments. Yet, the commonly accepted theory to-day is that of Möbius or that the thyroid hyperplasia in toxic goiter represents thyroid hypersecretion and that the hypersecretion is responsible for the toxic symptoms.

This last theory is based mainly on three lines of evidence: (1) symptoms similar to the syndrome of toxic goiter are produced in man by excessive thyroid administration; (2) patients with toxic goiter appear on the whole to be excessively sensitive to thyroid administration; (3) in many cases the symptoms of toxic goiter appear to be at least partly controlled by surgical and medical measures that reduce the thyroid volume and activity.

The most striking symptom of toxic goiter is the greatly accelerated metabolism. Du Bois has recently shown that in severe cases this may be increased 75 per cent. above normal, and an increase of 50 per cent. in moderately severe cases is not uncommon. In mild cases the state of metabolism may be practically normal. This author thinks that some of the other symptoms (tachycardia, high blood pressure, high temperature, nervousness) are in part secondary effects of augmented metabolism with its attendant increased production of heat. Du Bois also showed that there is no conservative form of treatment of toxic goiter that reduces the metabolism rate to any greater degree than mental and physical rest. These measures may lower the rate more than 10 per cent., while in some cases ligation of the thyroid arteries actually increased the rate of metabolism.

Experimental hyperthyroidism has not yet been produced. There is no evidence that the rat, fish, and opossum thyroids of Watson, Marine, McCarrison, and Bensley secreted in excess. It is true that excessive thyroid feeding, especially in man, duplicates most of the symptoms of exophthalmic goiter, but the same effects would probably be produced by any other substance that had a similar effect on the metabolism rate. It is biologically significant and clinically important that of all animals so far studied man is the most susceptible to the deleterious effects of thyroid

feeding. The attempt of Cannon to induce hyperthyroidism by union of the phrenic and cervical sympathetic nerves has already been referred to.

There are not wanting other interpretations of the nature of thyroid hyperplasia, especially in toxic goiter. The most important are the perverted secretion theory, and the compensatory hypertrophy theory, especially as elaborated and upheld by Marine. According to Marine the hyperplasia in goiter is a response of the thyroid to an increased need of the body for the secretion in consequence of some disarrangement in the general metabolism. That is, the hyperplastic thyroid secretes at a greater rate than the normal thyroid, but not at a rate greater than needed by the organism for the altered condition. In fact, according to Marine, despite the increased secretion in toxic goiter, there may be an actual thyroid deficiency owing to the greater need for the secretion. On this theory there is room for at least a careful experimental thyroid organotherapy in toxic goiter; and, in fact, favorable results from thyroid feeding in toxic goiter have been obtained by competent clinicians.

The nature of the thyroid hyperplasia in toxic goiter is, of course, bound up with the question of the cause of the hyperplasia. It will probably be found that we are dealing with a complex of causes (abnormal diet, deranged metabolism, specific infection, nervous disarrangements, etc.). That the hyperplasia in experimental animals is primarily due to changes in the blood appears to be shown by the recent experiments of Manley and Marine. The transplant of a normal thyroid into an animal with active thyroid hyperplasia becomes hyperplastic, and *vice versa*.

The interpretation of the nature of thyroid hyperplasia in toxic goiter is further complicated by the fact that in many of the lower animals thyroid hyperplasia histologically identical with that of toxic goiter in man is present without any other of the Basedow's syndrome. In fact, spontaneous Basedow as well as spontaneous cretinism is very rare though apparently not unknown in animals below man.

The justification of this rather lengthy discussion of hyperthyroidism in a chapter on organotherapy is our desire to clearly point out that the existence of actual thyroid hypersecretion with consequent symptoms of disease is still in question; also that it behooves clinical and laboratory workers to test anew prevalent theories, in the hope of reaching a clearer knowledge and a better control of a very serious malady, be it through organotherapy or other measures.

HYPOTHYROIDISM IN CHILDHOOD—CRETINISM

The most marked effect of the removal of the thyroid in young animals and of its atrophy or injury in children is a cessation of growth and development, both physical and mental. The changes in the skeleton are

especially marked,* there is a cessation or retardation of the normal ossification of the cartilages. The epiphyseal ends of the long bones grow slowly, while the periosteal ossification may be normal or in excess. The extremities are relatively short and thick; the pelvis is small. This condition and the muscular degeneration are responsible for the protruding abdomen. Abnormalities in the growth of bone are largely responsible for the characteristic shape of the skull and thorax in cretins.

If the thyroid deficiency does not occur until rather late in childhood,



FIG. 1.—CRETIN CHILD BEFORE (A) AND AFTER (B) TREATMENT WITH THYROID. (Bramwell.)

the above changes may be absent, and the hyperthyroidism be evident only in a cessation of normal growth.

The hair on the pubis and in the axillæ is scanty or absent, and the sexual organs are poorly developed; while puberty, if it occurs at all, is late. The skin in children is often myxedematous. Metabolism is much depressed (Bergmann, Mansfield, Du Bois); the oxygen absorption and nitrogen excretion may be but one-half that of the normal.

It is difficult, however, to distinguish between primary and secondary effects of injuries to the thyroid. The latter cause marked changes in the nutrition and metabolism, and these may be the immediate cause of some of the abnormalities now ascribed to the direct influence of the thyroid. There is evidence that hypothyroidism leads to increased growth of the hypophysis, the adrenals, and the islands of Langerhans in the pancreas. We cannot at present say whether or not these changes are compensatory in

* See, for example, Flinker; the opposite changes are found in conditions of hyperthyroidism in young individuals (Holmgren).

nature. The evidence seems to be to the contrary, at least as regards the changes in the hypophysis.

The effects of thyroid insufficiency upon mental development are no less striking than those upon physical development; the patients are apathetic, the expression is stupid, and idiocy frequent. There is evidence of degenerative changes in many of the organs and especially the muscle. The fatty degeneration of the muscle is at least in part responsible for the feeble heart, muscular weakness and characteristic "pot belly." There is also decreased resistance to infection, and, strange to say, increased susceptibility to thyroid administration.

Complete thyroidectomy in experimental animals appears to prevent sexual maturation entirely, and thus leads to sterility.



FIG. 2.—SPONTANEOUS CRETINISM IN A DOG, AGE EIGHT MONTHS. CYSTIC GOITER. (Carlson.)

The cretin symptoms following complete thyroidectomy in the young but otherwise normal animal do not appear until late after the operation (three to six weeks or longer). It is not clear that this means a persistence of the thyroid secretion in the blood for this length of time, but it is a fact that very small thyroid remnants suffice to maintain normal growth and health.

Spontaneous cretinism is rare in the lower animals. In man it is sporadic as well as endemic, and in either case it may be congenital or a matter of gradual development after birth (primary atrophy, cystic or colloid degeneration). The physiological state of the maternal thyroid during gestation influences the thyroid of the fetus. Thus, if the mother has marked thyroid hyperplasia during pregnancy the offspring is born with enlarged thyroid; on the other hand, simple colloid goiter in the mother has no influence on the fetal thyroids. It is also reported that complete thyroidectomy in the mother leads to thyroid hyperplasia in the offspring.

The thyroid hyperplasia of the young from mothers having active thyroid hyperplasia during pregnancy is probably not an instance of true inheritance, but a matter of fetal environment. The same conditions that induce the hyperplasia in the mother, acting through the blood, produce the same effect on the fetus. Hence it is primarily a humoral, not a nervous agent. But there may also be true inheritance factors in both simple and toxic goiter.

Hunter found that thyroidectomized sheep on starvation showed no starvation acidosis, but they excreted more nitrogen than the controls.



FIG. 3.—A NORMAL RABBIT AND TWO ABSOLUTE CRETINS FROM THE SAME LITTER. AGE THREE MONTHS. Control rabbit 1,630 grams; cretins, 760 and 840 grams. (Basinger.)

They showed no diminished oxidation, at least as regards purin catabolism, but the sugar tolerance appeared to be increased. Mansfield and Ernst state that there is no increased rate of protein catabolism in experimental fevers in thyroidectomized animals. According to Herring complete thyroidectomy in cats and rabbits has no effect on the epinephrin content of the adrenal glands unless parathyroid tetany develops, in which case there is a decrease in epinephrin. But in the cat, feeding large quantities of raw ox thyroid increases the epinephrin content in the gland by more than a third; Miura states that thyroidectomy does not influence alimentary and phlorhizin glycosuria in the animal, but diminishes somewhat epinephrin glycosuria. Contrary to earlier reports (Lorand) thyroidectomy does not appreciably influence pancreatic diabetes. Yuschenko has described certain changes in the phosphorous and lipid content of the blood and organs after thyroidectomy in animals.

HYPOTHYROIDISM IN THE ADULT—MYXEDEMA

Thyroid deficiency in the human adult is seen most typically in myxedema, which is characterized by physical and mental inertia, and by changes in the skin, depressed metabolism, etc. The skin is white and thickened, due to the growth of granulation-like tissue and an infiltration with a substance resembling mucin; the secretions are scanty or absent; the skin becomes dry and rough; and the hair falls out. There are frequently abnormal sensations of taste, smell and hearing. The temperature is subnormal and the pulse slow and weak. There are diminished oxygen absorption and carbon dioxid secretion; there is a tendency to obesity, although the patients usually eat little. The metabolism is depressed to a greater degree than in any other known condition.

Anderson reports a case of a woman whose metabolism was as low as 1,260 calories, or 18.8 calories per kilogram. After treatment for nine months with thyroid extracts the heat production rose to 2,099 calories, or 32.3 per kilogram, which are normal values. Du Bois reports a case of a cretin with a metabolism 20 per cent. below normal.

Nitrogen metabolism is also lowered; the daily excretion of urea is often less than 20 grams.

Lusk states that it is possible to explain the reduced temperature as due to disturbances in the nervous mechanism of temperature regulation, and that the lowered temperature may be an influence in reducing the metabolism of the cells. The coagulation time of the blood is stated to be shortened (Lidskey).

The effect of thyroidectomy on adult animals is variable. True myxedema is rarely, if ever, developed. Monkeys do not show conditions analogous to myxedema in human beings, at least for months or years after the operation (H. Munk, Kishi, Vincent and Jolly, Halpenny and Gun). Many adult animals show little change after removal of the thyroid, although eczema, conjunctivitis, rhinitis, and other indications of catarrh of the respiratory passages, and especially emaciation and diminution in the number of the red and increase in the number of the white corpuscles are common. There is lowered resistance to infection. Metabolism is depressed, carbohydrate tolerance is increased. Degenerative changes in the ovaries and testes have been described.

THYROID ADMINISTRATION IN HYPOTHYROIDISM

The most marked effects of the administration of thyroid are seen in cases in which the thyroid is absent or deficient, and it is upon the results in such cases that the therapeutic use of thyroid is based. Fresh or dried entire thyroid have so far yielded as good or even better results than various isolation products of the gland.

Administered in appropriate doses to cases of sporadic cretinism and infantile myxedema, there is at first a loss of weight, with improvement of the skin. Cyanosis disappears and the blood becomes normal. Growth, both bodily and mental, recommences and may take an almost normal course. The hair grows rapidly and becomes glossy; the teeth and nails also grow. There is a distinct acceleration of metabolism. The mental improvement is most marked in young children. Similar results are obtained in cretinoid animals (Piek and Pineles, Basinger, etc.).



FIG. 4.—MYXEDEMA IN ADULT BEFORE (A) AND AFTER (B) TREATMENT WITH THYROID. (Anderson.)

In complete absence of thyroid tissue no amount or duration of thyroid administration will bring the final growth up to the normal. *Thyroid organotherapy is therefore not a complete substitute for the living organ.* This is not surprising in view of the extensive degeneration found practically in all the organs in absolute cretinism.

Many attempts have been made to stimulate growth in conditions other than cretinism by thyroid administration. Thus, it has been extensively tried in idiots and backward children. It has been administered in cases of delayed union of fractures on the theory that it would hasten union by stimulation of specific bone metabolism.

Administered to cases of myxedema of cachexia thyreopriva, the myxedematous condition largely disappears. There is a marked increase in metabolism. The excretion of nitrogen in the urine may be increased 100 to 200 per cent. This increase results largely from the increased intake due to improved appetite, but there is usually a true loss of nitrogen. There are no striking changes in the partition of the nitrogen in the urine.

The consumption of oxygen may be increased 70 per cent. The temperature rises; the pulse rate is increased; there is usually a striking loss of weight due to the disappearance of the myxedematous infiltration and loss of fat. The entire metabolism is brought back to the normal level or raised slightly above the normal. The skin approaches the normal; sweating, which is usually entirely absent in myxedema, becomes possible. The hair grows again; menstruation reappears; the bowels become regular; the mental condition is much improved. These changes appear in three to four weeks with the usual doses.

The marked changes in the skin in cases of myxedema produced by the



FIG. 5.—SKIN LESIONS DEVELOPED IN THYROID-FED ABSOLUTE CRETINS FIVE MONTHS AFTER DISCONTINUING THE THYROID TREATMENT. (Basinger.)

administration of thyroid have led to the extensive trial of this substance in other abnormal conditions of the skin.

Mild Conditions of Hypothyroidism.—In addition to the above conditions, in which there is obviously severe thyroid deficiency, there are a number of conditions of hypothyroidism of a less severe type; Hertoghe and Kocher have laid especial emphasis upon these. Kocher states that many cases which have been treated for anemia, chlorosis, scrofula, nervousness, and disturbances of menstruation, seem to him clearly to be cases of thyroid deficiency. He also calls attention to the cases in which children show retarded growth with no apparent cause. The favorable results following the administration of thyroid make the diagnosis of the condition clear. Many of the cases of mild thyroid deficiency show, according to Kocher, very definite symptoms, among the most marked of which is a

feeling of inhibition preventing the subjects from accomplishing that which they desire. They are incapable of continued effort, such as reading, writing, and even speaking; they become shy and avoid society. They are indifferent to food, and neglect going to stool. Kocher states that remarkable improvement follows the administration of thyroid in such cases.

Kocher mentions many other symptoms due, as the effect of thyroid treatment appears to show, to slight thyroid deficiency. Among these are fatigue from slight exertion, although muscular development is good; slight swelling of the eyelids, lips, and cheeks; tendency to obesity, and the appearance of local accumulations of fat; swelling of the joints, so that patients frequently state that they suffer from gout or rheumatism; paresthesia, especially feelings of stiffness. Sometimes the skin has a yellowish tinge, suggesting chlorosis. Pigmentation of the skin is frequent, resembling that seen in pregnancy; the pigmentation in the latter condition may be due to relative thyroid insufficiency. This pigmentation often disappears under the influence of thyroid. Kocher raises the question if the effect of the thyroid in such cases may not be due to an effect upon the suprarenals or other organs of internal secretion.

Further changes in the skin and its appendages, upon which Kocher lays much emphasis, are dryness and coldness, with little tendency to sweating; the dryness of the hair and its tendency to fall out; the tendency of the nails to crack, and of the teeth to caries.

Kocher warns against ascribing more severe skin diseases to a condition of hypothyroidism, although he states that eczema, ichthyosis, etc., are especially prone to occur where the nutrition of the skin is deficient as a result of hypothyroidism.

Individuals with these mild degrees of hypothyroidism are sensitive to the cold. The coldness of the skin is due to sluggish circulation, which is also evident from the weak pulse.

Kocher states that marked improvement occurs in such cases as the above within a week or ten days, sometimes even in twenty-four hours, after beginning the administration of thyroid. Similarly beneficial results are stated to occur in the aged, when symptoms of thyroid hypofunction result from the gradual deterioration of the gland, and in pregnancy, when the thyroid may be unable to meet the increased demands made upon it.

Various chronic diseases and intoxications (tuberculosis, alcoholism, and sometimes syphilis) may injure the thyroid, so that a mild degree of hypothyroidism results; here again thyroid medication may be of benefit.

Stoeltzner states that rudimentary forms of infantile myxedema characterized by cessation of growth, excessive fatness, etc., are not uncommon; they sometimes follow infectious diseases or traumatism. In such cases thyroid causes some improvement. Simpson reports favorable results in many cases of infantile wasting. For children under nine months he began

with one-third of a grain of the dry gland once daily, larger doses sometimes causing diarrhea. Doses up to one grain daily were given to older children.

Effects upon metabolism, similar to but less marked and less constantly obtained, are produced when thyroid is administered to normal individuals and to normal animals. The effect in normal animals is largely a question of quantities of thyroid given, and of the species—man being the most susceptible. And there are great individual variations in the susceptibility to thyroid among apparently normal persons. The absorption of oxygen and the excretion of carbon dioxide may be increased 10 to 20 per cent., although in some cases there is no increase. The excretion of urinary nitrogen may be increased 20 to 50 per cent.; usually it is less, much depending upon the character of the diet. The change in nitrogen metabolism usually occurs first; that in total metabolism occurs later (in the course of two to three weeks). Increased destruction of protein cannot always be prevented by the administration of non-nitrogenous food. Hewitt reports, however, that fresh thyroid fed to adult rats in doses of 0.25 grain or less per day leads to increased food consumption and body weight, while larger doses have the opposite effect.

The excretion of phosphorus and of sulphur is also increased. There is, in man, usually a distinct increase in nervous excitability with attendant circulatory and other disturbances. Gudernatsch found that feeding thyroid to frog tadpoles greatly accelerates the metamorphosis while growth is actually retarded. This does not appear absolutely specific for the thyroid substance, as Morse obtained the same result with iodized blood albumin, and Abderhalden with thyroid protein hydrolyzed down to the amino-acid stage.

No other organ has such marked effects upon metabolism, and many attempts have been made to utilize these effects therapeutically.

The indications for the use of thyroid are clear in those cases in which there is a deficiency in the normal secretion; in other cases, however, its administration must be largely determined empirically, and it must first be shown that the type of increased metabolism induced by thyroid feeding is really beneficial in cases where there is not depression of metabolism due to thyroid deficiency. The mode of action of thyroid upon metabolism is obscure. Some believe that it stimulates the cells directly to increased activity; whereas others think that the effect is primarily upon various parts of the nervous system, the stimulation of which causes increased activity which results in increased metabolism. In support of the latter view Anderson and Bergmann state that there is no increase in the carbon dioxide output when thyroid is administered to a person kept in perfect quiet.

That excessive amounts of thyroid do increase nervous irritability is generally accepted on the basis of observations in Graves' disease and the

results of administering large doses of thyroid. Magnus-Levy believes that there are great individual differences, but that in some cases there is an increased metabolism of the resting cells. It is evident that the solution of this problem has important bearings upon the use of thyroid to influence metabolism; if the thyroid increases metabolism only indirectly by causing, through stimulation of the nervous system, increased activity, it could, for example, scarcely be considered a good treatment of obesity, at least in those forms in which thyroid deficiency is not a causal factor.

Excessive doses of thyroid have marked effects upon the circulation and nervous systems, but these are of interest chiefly in connection with the toxic action of the drug; they do not suggest any therapeutic use for it. Eppinger, Falta, and Rudinger attribute many of these effects to increased irritability of the sympathetic nervous system. Zondek and Frankfurter state that thyroid extract and iodothyrim cause bronchoconstriction and dilatation of the lung capillaries. Hoskins reports that thyroid feeding increases the growth of the thymus and decreases that of the adrenals.

For further discussions of the use of thyroid in hypothyroidism and goiter, see Vol. III, Sec. IV, Chap. VIII; and Vol. II, Sec. III, Chap. VII.

THYROID ORGANOTHERAPY IN OTHER CONDITIONS

For the *use of thyroid in obesity*, see Vol. II, Sec. III, Chap. VI.

Thyroid has been given in many other conditions that have not yet been distinctly shown to be caused by thyroid deficiency. In some of these thyroid deficiency is merely suspected; in others thyroid is apparently used because the symptoms resemble some of those occurring in hypothyroidism. Among these conditions are various disturbances of the skin, especially the dry scaly varieties. Thus it has been recommended in eczema, especially in that of early childhood and of old age; it has been used in psoriasis, chronic urticaria, pruritus, pemphigus, ichthyosis (Roux and Galippe), and scleroderma (Rocques). In the latter condition the thyroid has sometimes been found atrophied (Wells).

Thyroid treatment has been tried in the toxemias of pregnancy on the theory that the intoxication is due to thyroid deficiency. This theory is highly improbable, as the syndrome of hypothyroidism does not at all resemble pregnancy toxemias.

It has been recommended in various disturbances of the joints, such as arthritis deformans, irregular gout, chronic rheumatism, and indefinite "rheumatoid" pains (Steele-Perkins, Wilson, Stubenrauch, Pizarro). Among recent writers Levi and Rothschild have especially emphasized its value in certain forms of rheumatism of children; in these the thyroid is frequently enlarged (Clemens). It has also been used in certain cases of migraine and neuralgia, especially in those associated with menstruation.

Thyroid has found extensive use in various disorders of menstruation (Goodall and Conn). Experimental and clinical work has shown that the thyroid is necessary for the proper development of the genital organs and for menstruation. Further relations between the thyroid and the female sexual organs are suggested by the more frequent occurrence of myxedema in women after the climacteric—especially in those who have borne children, the more frequent occurrence of exophthalmic goiter in women, and by the enlargement of the thyroid during menstruation and pregnancy. It has been recommended in amenorrhea when other causes cannot be detected, and especially if there is a tendency to obesity or myxedema. Thyroid in large doses has been recommended in eclampsia; the beneficial effects were attributed in part to the diuretic action.

The influence of the administration of thyroid upon the defective

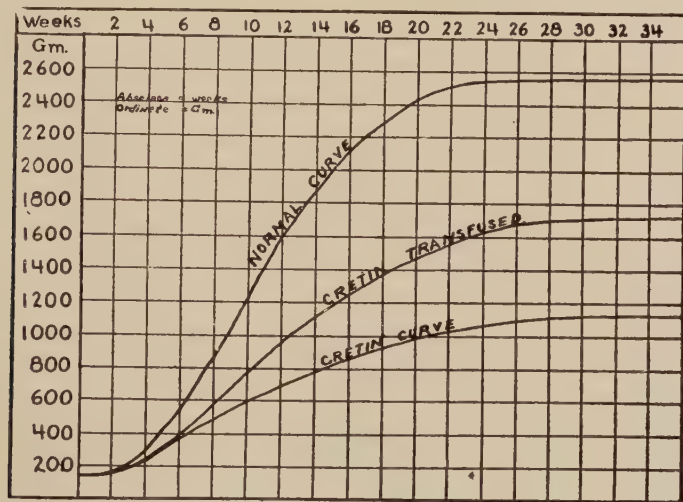


FIG. 6A.—GROWTH CURVES OF FOUR NORMAL AND THREE ABSOLUTE CRETIN RABBITS, SAME LITTER. (Basinger.)

growth of bone in cretinism suggested its use in delayed union of fractures; some writers have reported favorable results. Bircher reports that the administration of thyroid to young animals delayed bone growth; this was probably due to excessive doses. He does not believe that the effect on bone growth in cretinism is specific. Thompson and Swarts, contrary to some, did not find that removal of the thyroid delayed the healing of fractures. It has been said to have good results in rickets (Variot and Pironneau). Glosse proposes the theory that arthritis with accompanying disturbances of protein metabolism is due to lack of thyroid secretion, which he considers, under normal conditions, to act as a deamidizing agent.

Good results have been reported from the use of thyroid in hemophilia (Rugh). It is said that the preliminary administration of the drug ren-

ders necessary operations (extraction of a tooth, for example) safer. Such results must be doubted, for the coagulation of blood is said to be distinctly

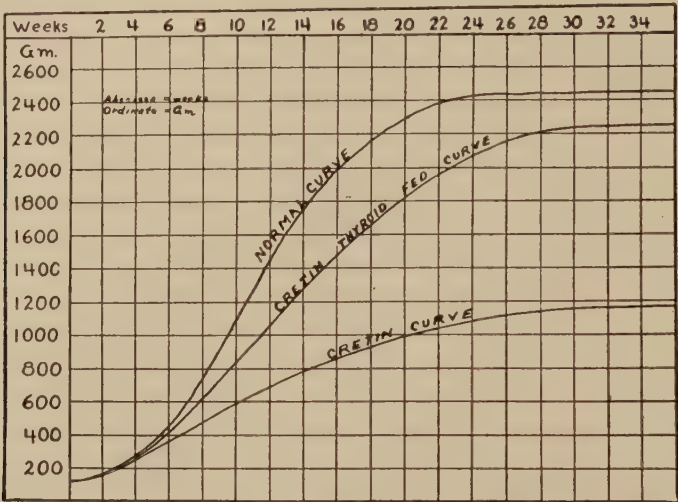


FIG. 6B.—GROWTH CURVES OF FOUR NORMAL CONTROL RABBITS, FIVE ABSOLUTE CRETINS, AND EIGHT ABSOLUTE CRETINS FED STANDARD U. S. P. THYROID EXTRACT. (Basinger.)

delayed in Graves' disease and experimental hyperthyroidism (and to be accelerated in conditions of hypothyroidism). Frazier and Peet have

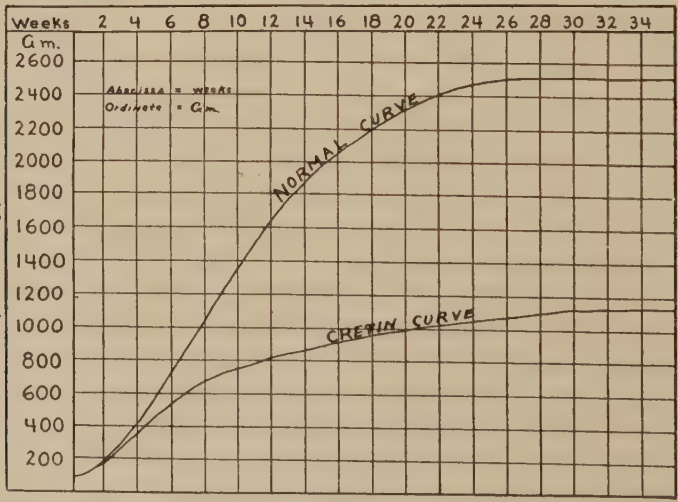


FIG. 6C.—GROWTH CURVES OF FOUR NORMAL CONTROL RABBITS, TWO ABSOLUTE CRETINS, AND SIX ABSOLUTE CRETINS TRANSFUSED REPEATEDLY WITH HYPERTHYROID BLOOD SERUM. (Basinger.)

recently reported the cure of a case of internal hydrocephalus by thyroid administration. They were led to use this treatment by their laboratory

findings that thyroid extract decreases the rate of formation of cerebrospinal fluid. This observation is erroneous (Becht and Mattill). There is no evidence that the internal hydrocephalus case of Frazier and Peet would not have improved equally well without the thyroid treatment. On the hypothesis that the thyroid secretion aids the body against infection Bordley recommends the use of thyroid in malignant uveitis. He reports both good results and failures.

The marked mental changes produced by the administration of thyroid in myxedema and cretinism have led to the use of thyroid in various other types of insanity, mental disturbances, epilepsy, etc. (Goodall, Bhiday, Boltin). The results in certain cases of beginning melancholic insanities are stated to have been good. It is interesting to note in this connection that a very large percentage of patients with mental diseases have abnormal thyroids (Peabody, Werelius), and that Grafe has found in certain mental diseases a true retardation of metabolism (heat production 39 per cent. below normal, for example) which is suggestive of a condition of hypothyroidism. Ross administered thyroid to four dementia precox patients and found an increased excretion of total nitrogen and of creatinin.

Space does not permit, and in many cases the clinical reports are too incomplete, to evaluate the alleged favorable results of this purely empirical thyroid organotherapy, but the following comments seem warranted: (1) If there is in the patient sufficient hypothyroidism to induce amenorrhea, mental disorders, skin lesions, defective bone metabolism, lowered resistance to infection, etc., there must be other indubitable signs of thyroid deficiency. (2) Unless these conditions are due to hypothyroidism administration of thyroid to these patients will, on the theory of Möbius, *induce a state of hyperthyroidism*, and there is no evidence that this condition has a favorable influence on any malady. (3) There is no evidence that the augmented metabolism induced by thyroid administration is beneficial in any other condition than cretinism and myxedema. Moreover, a general increase in body metabolism can be induced by dietetic and hygienic measures, cold baths, exercises, etc. (4) When the failures are balanced against the favorable results in all cases of empirical thyroid organotherapy there is little basis left for the belief that the thyroid treatment is really responsible for the latter.

Methods of Administering Thyroid

Transplantation.—The earliest attempts to combat thyroid deficiency were by the transplantation of normal thyroid. This method has succeeded when the thyroid is transplanted to another region of the same individual; it has been less successful when the gland is transplanted from one animal to another of the same species. It is therefore of experimental but of little or no practical importance. It has been recom-

mended in cases in which other forms of substitution therapy fail. Kocher states that one advantage of transplantation is that the body can regulate the amount of secretion according to its needs, but that is not true of a thyroid graft from another individual even under the most favorable conditions (Manley and Marine).

Subcutaneous Injections.—Murray (1891) introduced the method of treating myxedema by the subcutaneous injection of glycerin extracts of thyroid; the extracts were obtained from sheep and calves, and were preserved with phenol. They frequently caused severe local reactions. This method has no advantage over feeding the thyroid by mouth, but many disadvantages. It cannot be recommended at least until the active thyroid substance has been isolated in pure form.

Administration by the Mouth.—A very important advance in thyroid medication was made in 1892, when Fox, Mackenzie, and Howitz almost simultaneously announced that favorable results could be obtained in myxedema by the administration, *per os*, of the fresh or cooked thyroid. The use of cooked and fresh glands was soon practically replaced by the use of the dried glands, and of various extracts. Some of these have received recognition in various pharmacopeias.

OFFICIAL AND OTHER PREPARATIONS OF THYROID

Pharmacopeial Preparations.—Desiccated thyroid gland is recognized in the United States Pharmacopeia (VIII, 1905) under the name *Glandulae Thyroidae Siccæ*. It is directed to be obtained from the sheep and to be freed of fat, and powdered; one part represents approximately five parts of the fresh glands. Tests are included to insure the presence of iodine in organic combination and the absence of inorganic iodine. The average dose is given as 0.25 gram, or four grains.

The Belgian Pharmacopeia (III, 1906) recognizes thyroid in various forms. It is stated that sugar of milk should be added to the dry thyroid or its extracts, so that the weight equals that of the fresh gland from which it is obtained; a gram of the fresh gland or the equivalent in the dried or extracted form contains about 0.0003 gram of iodine. This corresponds to about 0.15 per cent. iodine in the dried gland.

The British Pharmacopeia (1898) recognizes two preparations of thyroid, the dry (*Thyroideum Siccum*) and the solution (*Liquor Thyroidei*). The former is directed to be dried at 32.2° C. to 37.8° C. and to have the fat extracted; the dose is given as three to ten grains. The solution is prepared by macerating the glands (of sheep) with equal parts of glycerin and a 0.5 per cent. solution of phenol, straining and adding sufficient of the phenol solution to make six c.c. for each entire gland used. It is to be freshly prepared; dose, five to fifteen minims (which is equal to one-sixth to one-twentieth of an entire gland).

Tablets.—At present thyroid is administered, at least in this country, chiefly as the dried powder which is usually prescribed in the form of tablets. Such tablets are very convenient and satisfactory if they are well chewed, but their use has led to the utmost confusion as to dosage. Many physicians both here and abroad speak of prescribing so many “tablets” without, as a rule, specifying either the size of the tablet or the maker; others speak of prescribing “two” or “five-grain tablets,” without specifying whether the weight refers to the total weight of the tablet (that is, the thyroid plus the excipient), or to the thyroid alone, and, in the latter case, as to whether the weight refers to the fresh or dry gland. Others specify some manufacturers’ “tablets” without further particulars. How inexcusably inexact are such procedures is evident from such facts as the following: Many manufacturers prepare several “tablets” of different sizes; one firm, for example, lists “one-half, one and one-half, two and one-half, and five-grain, and one-tenth and three-tenths-gram tablets”; which of these tablets the patient received when the physician states that he administered this firm’s tablets it is usually impossible to determine.

The confusion as to dosage is still further increased by the fact that different firms use different methods of expressing the amount of thyroid in their tablets. Thus, one firm’s “five-grain tablet” contains two grains of desiccated thyroid; another firm’s “five-grain tablet” means that each tablet contains the equivalent of five grains of the fresh gland. One firm’s “two-grain tablet” means that each tablet is equivalent to ten grains of the fresh thyroid; another firm states that one grain of their dry thyroid represents eight grains of the fresh gland. There can be little doubt that, when some physicians write of prescribing a five-grain tablet of dry thyroid, they really prescribe a tablet containing the equivalent of five grains of fresh thyroid, or one-fifth of what the reader may be led to suppose.

Since some commercial “tablets” contain twenty times as much thyroid as other “tablets,” and since some preparations of thyroid are four times as active as others, there is a *possibility* of one “tablet” being equal, physiologically, to eighty other “tablets.” *

Extracts and Other Preparations.—In addition to the above, there are a number of extracts and other preparations of the thyroid on the market. The term “extract” is frequently applied to the dried powder, a practice often leading to confusion.

Thyroidin-Merck, a preparation to which reference is frequently made in the literature, is dried thyroid, four-tenths gram of which is equivalent to one fresh sheep thyroid of medium size; one part represents about six parts of the fresh gland.

Thyroidin-Notkin is a preparation of the proteins of the thyroid,

* The above remark applies to the tablets on the American market. Equally great confusion prevails in regard to other “tablets” on foreign markets; thus in one case a one-tenth-gram tablet contains one-fourth of a medium sized thyroid of a sheep.

stated to be especially useful for hypodermic injection. The dose *per os* is one-sixth of a grain; hypodermically, 15 minims of a five-tenths per cent. solution.

UNTOWARD EFFECTS AND CONTRAINDICATIONS

Untoward effects not infrequently follow the medicinal use of thyroid. There are, however, great individual differences in susceptibility. Children are stated to be less sensitive than adults; patients with myxedema and toxic goiter are especially sensitive. This applies also to experimental cretins. Even the eating of salt water fish (because of the iodine content?) is said to aggravate toxic goiter (Grumme).

Among the milder symptoms reported from overdoses, or the long-continued use of smaller doses, or in especially sensitive individuals, are flushing with increased sweating, fullness of the head with palpitation of the heart, tachycardia and anginous pain in the heart, dyspnea, faintness, dizziness, loss of appetite, loss of body weight, etc. Such symptoms have followed the taking of two grains of the dry powder. Other symptoms are nausea, vomiting and severe diarrhea. Foulis reported a case of profuse fatal diarrhea following the first dose of one-fourth of a lobe of thyroid in twenty-four hours. Glycosuria frequently occurs. Marked nervous disturbances may occur. In addition to the palpitation, etc., there may be great restlessness and sleeplessness, irritability, tremors, pains in the back and extremities, and even delirium. The temperature is sometimes elevated. Urticaria and other disturbances of the skin may occur. Great emaciation, long-continued debility, and anemia have been reported; the urine may be diminished, although, as a rule, thyroid has a diuretic action. As a rule these untoward effects subside within a few days after stopping the thyroid treatment, but Krecke reports that he has seen emaciation, tachycardia, and excitement continuing for a year after the administration of thyroid to patients with Graves' disease.

In cases of rapid growth under treatment, bow-legs have sometimes been reported; in such cases the doses should be immediately diminished.

A number of fatal cases have been reported from ordinary or small doses.

A condition very similar to exophthalmic goiter has been reported a number of times following excessive use of the drug. Von Notthaft reported such a case where an obese man took nearly one thousand "tablets" in five weeks; the symptoms slowly subsided when the drug was discontinued.

A large number of accidents, some of them fatal, have occurred from the use of thyroid in obesity. It is especially dangerous to obese patients with a tendency to cardiac or aortic disease. It is also contra-indicated in obese patients with a tendency to diabetes.

Summary

1. Thyroid organotherapy is definitely established in all conditions of hypothyroidism. The administration of the entire gland substance by mouth in doses that must be determined for each individual patient is the best method of procedure. But we should insist on chemical and physiological standardization of the thyroid products.

2. Because of the present uncertainty as to the cause and significance of the thyroid hyperplasia in toxic goiter thyroid administration may be tried experimentally in these conditions, especially in the very early and in the later stages.

3. If we assume, with Möbius, that an excess of thyroid secretion in the blood produces the untoward symptoms of toxic goiter, it follows that an increase of thyroid secretion above the normal is injurious. Hence, it is evident that thyroid administration is contra-indicated in all conditions *not* due to thyroid deficiency, for by giving thyroid in such cases, we necessarily increase its concentration above the normal in the body fluids. The results obtained by thyroid organotherapy in various diseases other than hypothyroidism do not appear to justify further clinical empiricism in that direction until well controlled laboratory tests have established new lines of attack.

4. The various theories ascribing to the thyroids specific inhibitory or stimulating functions on other endocrine organs have so little basis in fact that there is no justification for thyroid administration in cases of supposed hyper- or hypo-activity of such organs, or general disturbance of internal secretion equilibrium.

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THE PARATHYROIDS

Physiology.—The parathyroids, like the thyroid gland, develop from the epithelium of the embryonic gill arches. In man and most mammals the parathyroids are either imbedded in the thyroid gland, or lie close to the thyroid capsule. There are usually two pairs of thyroid glands in man and mammals in general, but accessory parathyroids are frequently present in the thymus, and associated with accessory nodules of thyroid tissue both in the neck and the chest. The glands were discovered by Sandstrom in 1880, but their specific rôle was not recognized by physiologists and clinicians until a much later date. Because of the situation of the parathyroids in or on the thyroid gland, complete thyroidectomy involves, in most mammals, also complete parathyroidectomy, and the characteristic syndrome developing as a result of parathyroid extirpation were for many years erroneously described as due to deficiency of the thyroids.

The striking thing is the relatively small amount of total parathyroid tissue in animals, and the serious effect that develops promptly on the extirpation of the glands. Histologically the parathyroids are made up of columns of epithelial cells, without acini or colloid, so characteristic of the thyroid gland. Vincent and his pupils have reported that on extirpation of the thyroids the parathyroids develop into typical thyroid structure. Vincent has adduced other evidence in support of his theory that the parathyroid glands represent an embryonic state of the thyroid. But Vincent's experimental results have not been substantiated by other investigators. It is certain that in the rabbit complete thyroidectomy does not cause the parathyroids to assume the structure and function of the thyroid (Basinger). The functional independence of the thyroid and the parathyroids is further shown by the absence of iodine in the parathyroid gland. The earlier workers who reported iodine in the parathyroids were not careful to exclude traces of thyroid tissue. This is practically impossible, if one uses the parathyroids that are embedded in the body of the thyroid gland.

While it is generally assumed that the parathyroids produce an internal secretion, this theory rests on a very slight foundation of facts. It is a fact that complete extirpation of the glands leads quickly to the development of grave and fatal symptoms, but we do not know how the living parathyroids control the vital processes so that these symptoms are held in abeyance. Berkeley and Beebe report that they have isolated a specific nucleoprotein from the parathyroids, and that this nucleoprotein is capable of counteracting some of the effects of parathyroid extirpation. These findings have not been substantiated.

Extirpation of the Parathyroid.—Practically all that is known of the

functions of the parathyroids has been learned from the extirpation of these glands in animals and man. The typical symptoms in animals are as follows: There is a latent period of several (twelve to forty-eight) hours in which the only symptoms may be a loss of appetite, some increased thirst, and a condition of hyperirritability of peripheral nerves. Then appear unrest and fibrillary contractions of various muscles, especially of the tongue and jaws; these become more frequent and are accompanied by a stiffness of the extremities and clonic contractions of groups of muscles. The clonic contractions then extend to all the muscles, leading to the typical tetanic attacks, which are accompanied by salivation and increased cardiac and respiratory activity, and, in most animals, a rise in temperature. These attacks are succeeded by a condition of prostration, during which the dyspneic respiration gradually returns to normal. The animals may apparently completely recover, but, within a few hours or a day or two, new attacks develop and death occurs. The duration of life after complete removal of the parathyroids rarely exceeds ten to fourteen days.

If only two or three parathyroids are removed, there may develop a condition of latent tetany; in this there are often no symptoms except under special conditions. Among the influences provoking attacks of tetany in such animals are the occurrence of pregnancy or lactation, in some species, though the administration of various poisons may also provoke an attack.

The rate of development and the final degree of the increased excitability of the motor neurons following parathyroidectomy in the dog are not appreciably influenced by ablation of the cerebral motor cortex, spinal transection, or section of the dorsal nerve roots. The increased excitability is therefore probably due primarily to some direct chemical action on the motor neurons.

The course of the parathyroid tetany is not appreciably influenced by ablation of the motor cerebral cortex, or by rendering a limb atonic through section of its afferent nerves.

As the epileptic spasms or tetanic attacks following removal of the parathyroid glands do not develop posterior to the spinal transection, it would seem that the actual tetany depends, not only on the local increase of motor excitability in the spinal cord, but also upon nervous connections with some region of the encephalon below the cerebral cortex (Mustard).

Wilcox found that removal of one to two or three of the parathyroids in dogs may induce more or less permanent hyperexcitability of the nerves, but no tremors or tetany, even during pregnancy or lactation. But it is significant that the nervous hyperexcitability became more marked during pregnancy, and especially during lactation. When all the parathyroid tissue is removed in the dogs the hyperexcitability of the peripheral nerves

is in evidence one to three days before the appearance of tremors and tetany.

In some cases of parathyroidectomy cachexia and depression appear at the very onset, without any evident period of nervous hyperexcitability. This is particularly frequent in cats. The cachexia and depression is usually accompanied by subnormal temperature. Practically all animals that survive the violent attacks of tetany and pyrexia die in cachexia and depression.

Parathyroid Tetany and the Digestive Tract.—Parathyroid tetany in dogs is accompanied by gastro-intestinal disorders: anorexia, vomiting, diarrhea (usually), pain in the abdominal region, and in the majority of cases hyperemia, hemorrhages, and ulcers of pyloric and duodenal mucosa. The hyperexcitability of the peripheral nerves in dogs in parathyroid tetany is usually, but not always, shown by stimulation of the phrenic nerves by the action current of the heart.

Falta or Kahn describe cases of tetanic contraction of the stomach in human tetany. There are no spasms, contractures or other evidence of hyperexcitability or tetany of the neuromuscular mechanisms of the digestive tract in parathyroid tetany in cats and dogs. Even in very severe tetany the movements of the stomach and intestines may be normal; the deviation from normal is in the direction of depression or paralysis. The gastric and pancreatic digestion in tetany may be normal, but it is usually retarded. The retardation may amount to practical failure of digestion. In very exceptional instances there may be acceleration of the gastric digestion (cats). The retarded digestion is not due to the absence of appetite secretion or to splanchnic inhibition; it is probably due either to direct action of substances in the blood on the digestive glands (secondary effects) or to altered activity as a direct effect of the absence of the parathyroid secretion. In the case of other sympathetic and autonomic mechanisms (cervical sympathetic, pilomotor, sweat nerves, the uterus, the bladder, the sphincters) the deviation from normal activity in parathyroid tetany in cats and dogs seems also to be in the direction of depression.

In cats and dogs Keeton found a diminished secretion of gastric juice during parathyroid tetany, and the juice contains less than the normal amount of pepsin and hydrochloric acid. This impairment of the gastric secretion is, on the whole, directly proportional to the severity of the tetany. Stoland found that the quantity of the pancreatic juice and the bile secreted is also greatly diminished in tetany.

The hunger contractions of the empty stomach in parathyroidectomized dogs are depressed in direct proportion to the severity of the tetany. In extreme tetany the empty stomach is atonic and dilated. This is probably a factor in the characteristic anorexia of tetany animals.

The condition of the digestive tract in experimental parathyroid tetany

is of great interest, in view of the various types of tetany of gastro-intestinal origin in man. While it has been known for a long time that feeding meat to parathyroidectomized animals hastens and intensifies the tetany symptoms, and that starvation retards and diminishes the tetany symptoms, it is nevertheless probable that the gastro-intestinal symptoms of parathyroid tetany in animals are the effects and not the primary cause of the tetany syndrome.

Parathyroid Tetany and the Liver.—Various changes in the blood and in the urine (glucosuria, acidosis, increase of ammonia and of amino-acid nitrogen in the urine, etc.) reported by a number of observers in tetany animals have naturally directed attention to the liver. Carlson and Jacobson called attention to the marked similarity of parathyroid tetany, the tetany of ammonia intoxication, and the nervous hyperexcitability produced by meat feeding in dogs with the blood shunted past the liver into the general circulation by the Eck fistula. There is some histological evidence of liver degeneration of animals dying in tetany; and in the clinical tetany of pregnancy (eclampsia) there appear also to be instances of liver involvement. But extensive investigations on tetany dogs have so far failed to disclose any primary liver depression of importance, except a diminished secretion of bile, and this is probably due to the condition of the digestive tract rather than to the absence of specific parathyroid secretion.

During parathyroid tetany there is no change in the sugar tolerance (Stoland, Miura); the excretion of ammonia and amino-acids in the urine is normal, or less than normal in early tetany (Wilson, Stearns and Janney); the blood fibrinogen is normal or greater than normal. The formation of fibrinogen is one of the functions of the liver, hence the use of the blood fibrinogen as a test of liver function. But in as much as the secretion of bile is decreased, functional liver test depending on excretion of pigments in the bile would probably disclose, erroneously, a liver depression in tetany animals. Of course, it is obvious, that when the tetany condition has rendered the animal moribund, the liver will be depressed along with the entire organism. This is of no significance. The question of importance is whether there is any evidence of liver depression that can account for the genesis of the tetany itself. Such liver changes have not yet been demonstrated.

The Blood in Parathyroid Tetany.—The literature on this most important phase of parathyroid physiology and pathology is conflicting. MacCallum and Voegtlin reported a marked acidosis, with a decrease of the calcium salts of the tissues and the blood and an increased excretion of calcium in the urine. None of these results has been confirmed (Cooke). Bergheim, Stewart, and Hawk report a case of probably complete parathyroidectomy in a man with slight retention of calcium salts. In later experiments MacCallum reported that transfusion of the blood of

tetany dogs through the leg of a normal dog raised the excitability of the motor nerves of the transfused leg, while similar transfusion of normal blood through the leg of a tetany dog reduced the excitability of the nerves of the tetany leg. If these observations are confirmed, they would seem to prove that in parathyroid tetany there is some change in the blood (e.g., some toxic substance) that induces the nervous hyperexcitability by direct action on the nervous tissue. It does not appear that Dr. MacCallum controlled the *temperature factor* of the transfused blood. Fever blood will, of course, raise the excitability of the nerves, by the temperature factor alone.

In connection with MacCallum's theory of calcium deficiency, it is interesting to note that Thompson, Leighton and Swarts, and Morel have found that traumatism of bone prevents tetany from removal of the parathyroids; it does not, however, prevent the development of cachexia.

Peterson, Jobling, and Eggstein report a diminution of the serum lipase, a gradual increase in the non-coagulable nitrogen and proteoses of the blood and an increase in the aminonitrogen at the height of the tetany. Cooke and Greenwald report an increase in the undetermined urine nitrogen. According to Greenwald there is a marked retention of phosphorus after parathyroidectomy, and this is accompanied by retention of sodium and potassium. But sodium or potassium phosphates are not sufficiently toxic to be the agent of the tetany.

Greenwald also showed that xanthin and inosinic acid are not the toxic agents, for there is not enough of either of these substances in the blood or tissue of tetany animals to cause symptoms, although intravenous injections of large amounts of xanthin cause convulsions. The significance of the phosphorus retention in parathyroid tetany is as yet unexplained; but the work of Erdheim and others indicates that chronic parathyroid deficiency leads to impairment of bone growth.

W. F. Koch and Paton, Findlay and Burns report that there is an increase in the excretion of methyl cyanids, and trimethylanin, or guanidin in the urine of tetany dogs. Injection of these substances into animals induces symptoms apparently identical with parathyroid tetany. But there is no evidence that there is sufficient concentration of guanidin in the blood to induce the tetany in parathyroidectomized dogs. Using biological tests, several observers have reported an increased toxicity of the urine of tetany animals. We have seen that some of the earlier investigators reported a condition of acidosis in tetany.

Wilson, Stearns and Janney find, on the contrary, that after parathyroidectomy there is a primary alkalosis, or greatly increased alkalinity of the blood, and that acidosis is a secondary effect of the severe tetany owing to the formation of acids in the muscular contraction. These observers advance the theory that the alkalosis is the primary factor in the tetany, and support this view by the fact that giving of alkalis increases

the tetany, while administration of acids decreases the tetany. The reader will recall that MacCallum found similar support for his theory of primary calcium deficiency in the fact that calcium injections decrease the tetany symptoms temporarily. Acids, as well as calcium salts, depress the nervous tissues, but this drug action does not prove the primary relation of alkali excess or calcium deficiency to the genesis of parathyroid tetany.

The Control of Experimental Parathyroid Tetany.—Some of the earliest investigators of the physiology of the parathyroids (Lusena, Vassale, Generali, Moussu, MacCallum) reported that the tetany could be checked by the injection (subcutaneous, intraperitoneal, or intravenous) of emulsions of the parathyroids; favorable results were also reported from the feeding of the gland. Berkeley and Beebe report that the active part of the gland is the nucleoprotein fraction; this is efficient when given by the mouth, but much more so when given subcutaneously.

The treatment of parathyroid tetany, by the administration of the parathyroid glands, differs in important particulars from that of myxedema by the administration of thyroid. The effect of thyroid is strictly specific; no other gland, substance, or method will relieve the symptoms. It has been found, on the other hand, that parathyroid tetany can be temporarily checked, at least in the early stages, by the administration of salts of calcium, magnesium, strontium, and barium; by the injection of large amounts of sodium chlorid solution; by the injection of acids; by injection of extracts of the thyroid, the thymus, the pancreas, the testes, and the hypophysis; by the injection of proteoses or peptones; by the injection of hypertonic sugar solutions; by the administration of amyl nitrate, etc. In dogs the early attacks of parathyroid tetany can usually be decreased or prevented by giving the animal a cold bath, reducing the pyrexia. Transfusion of normal blood into parathyroid tetany dogs decreases the tetany but little, and does not lengthen the life of the animal.

Giving parathyroids by mouth appears to be entirely useless in the hands of later investigators (MacCallum and Voegtlin, Marine). Marine gave as many as one hundred fresh parathyroids per day to dogs with complete tetany without amelioration of the symptoms or prolongation of life, but transplantation even of a single parathyroid from another species controlled the tetany for a few days, or until the gland was completely absorbed.

It appears that, with the exception of parathyroid transplantation, all measures that have so far proved efficient in suppressing the parathyroid tetany symptoms are only temporary palliatives. Their action is complicated by the spontaneous periodicity of the symptoms in the early stages of the disease. The efficiency of these measures varies indirectly with the stage of the cachexia and the severity of the excitation symptoms.

It appears that, with the exception of parathyroid transplantation, the action of all measures that suppress the excitation symptoms can be ac-

counted for by *decreased excitability*, primarily of the nervous tissues. The excitability is decreased *directly* by the drug action of the calcium and the strontium salts and by hypertonicity; indirectly by substances or measures that cause partial anemia of the brain through vasodilatation (tissue extracts, albumoses, amyl nitrite, stimulation of the depressor nerves). None of these measures has therefore any *specific* significance as regards the cause and nature of parathyroid tetany.

In most of the experiments administration of the above substances has relieved the symptoms of tetany only, the animals dying later in cachexia; the cases of complete recovery are due to hypertrophy of accessory glands. Thus, valuable as the administration of the gland or salts of calcium may be in checking the symptoms of tetany and in prolonging life, it is open to question whether it is possible to obtain permanent cures in complete parathyroidectomy, except by implantation of a living gland.

For the permanent relief of parathyroid insufficiency transplantation of the glands is the only effective measure, but the results have been disappointing (Halsted, Leischner and Köhler, Landois, Marine, and others). Halsted concludes that transplantation succeeds only when a parathyroid deficiency has been previously induced, and that parathyroid tissue transplanted in excess of what is urgently required by the organism does not live.

Parathyroid Deficiency in Man.—The clearest cases of parathyroid insufficiency in man are those in which the glands have been more or less completely removed or injured at operations. Cases of this character are now rare, but occasionally occur (Pool, Branham, Erdheim) as a result of accident, especially from an interference with the circulation of the glands (Halsted). The symptoms of postoperative tetany in man are very similar to those described in animals. If death does not occur in a short time, a chronic condition of latent tetany or of subtetanic hypoparathyreosis (Halsted) develops. Such a condition may continue for years, with chronic nervous hyperexcitability (Erb, Chvostek, and Trousseau signs), the patients having attacks of tetany at irregular intervals.

Another form of tetany, in which a condition of parathyroid insufficiency may exist, is that which occurs in pregnancy or lactation; at other times there may be no evidence of tetany. This form is strikingly like that observed in parathyroidectomized animals; it has also been observed in women after operations on the thyroid (Frank). Krabbel reports the case of a girl who for seven years had tetany only during menstruation; she was completely relieved by the implantation of parathyroids into the tibia.

Another form of tetany, the etiology of which is still obscure, is that of children. A number of writers have reported finding extensive hemorrhages into the parathyroid glands in this condition. Others, however,

state that such hemorrhages are comparatively common in infants, and maintain that they are found as frequently in children who do not show tetany symptoms during life as in those who do (Auerbach). Extensive hemorrhages into the parathyroids have been reported in cases of sudden death, with spasms, of children (Grosser and Betke). Haskins and Gerstenberger found no evidence of parathyroid involvement in infantile tetany.

Attempts have been made to bring tetany of gastro-intestinal origin, toxic tetany, and those forms associated with various nervous diseases, into relation with the parathyroids. Parathyroid deficiency has been suspected to be a factor in paralysis agitans, myotonia congenita, myoclonia, chorea, osteomalacia, rickets, and eclampsia, but nothing conclusive has as yet been demonstrated.

Greenwald's studies on the blood of paralysis agitans patients do not support the theory of parathyroid genesis of this disease.

Spontaneous atrophy or hypertrophy of the parathyroids in man have not been definitely established, but they probably occur. Gjestland reports hyperplasia of the parathyroids in Parkinson's disease. Roussy and Clunet report parathyroid hyperplasia in paralysis agitans. Where there is sufficient atrophy or destructive lesions of parathyroids the condition of varying degrees of tetany will certainly be in evidence. *But none of the various types of clinical tetany (eclampsia, infantile, gastro-intestinal tetany, paralysis agitans, etc.) have so far been definitely shown to be due to parathyroid deficiency.* Parathyroid organotherapy of these maladies is therefore at present purely experimental and empirical.

PARATHYROID ORGANOTHERAPY

Efforts to control the tetany following the removal of the parathyroids, or the effects of interference with their blood supply by the administration of parathyroids, have met with variable degrees of success. Halsted states that, in a patient suffering greatly from subtetanic hypoparathyroidism as the result of two operations upon a large goiter, tetany had for three years been averted and the status parathyreoprivus made endurable by the feeding of parathyroids, by hypodermic injections of the nucleoproteins of the parathyroid gland, and for almost one year by the administration of calcium lactate. At the beginning six dried bees' parathyroids were given every three hours; the effect "was almost instantaneous and most marvelous." The dose was then reduced to one gland three times daily; further reduction could not, for several weeks, be borne. Later fresh glands were substituted; these were more readily taken than the dried ones.

Branham used subcutaneous injections of emulsions of beef parathyroids with success in a case following operation for goiter; the tetany

disappeared permanently after a second injection. It is evident that this patient would have recovered without the parathyroid treatment.

Schneider reported a case of postoperative tetany in which the administration of the dry parathyroid of the horse (0.02 gram in two days) was followed by improvement; the symptoms later reappeared, but disappeared after 0.03 gram of parathyroid. Other favorable reports have recently been published by Bircher, Rossiysky, and others. Eschrich, Frankel-Hochwart, Pineles, Rensburg, and others report negative results from parathyroid therapy in human parathyroid tetany.

Several cases have been reported in which relief or cure of post-operative tetany followed transplantation of the gland. Leischner and Köhler obtained only temporary relief from transplantation in one case, and no results in another. They suggest that in some of the apparently successful cases of transplantation in man there was a regeneration or recovery of function by the remnants of parathyroid tissue of the patient.

Parathyroid has been administered with inconclusive results in a number of other forms of tetany and in other conditions; the influence of suggestion has not always been eliminated. Haskins and Gerstenberger obtained no effects from parathyroid and calcium administration in one case of infantile tetany.

Berkeley relieved the symptoms of *gastric tetany* by the administration, by mouth, of fresh beef parathyroids; Moffitt also reports favorable results from the use of the dried powder, and later from hypodermic injections of the nucleoproteid of beef parathyroids.

Loewenthal and Wiebrecht obtained good results from parathyroid feeding in infantile tetany; but others have reported entirely negative results.

Berkeley reports better results from the administration of parathyroid in *paralysis agitans* than from any other remedy. The treatment should be long continued. Of twenty-six cases treated, five were not benefited, three showed temporary improvement, and eighteen grew progressively better during the whole period of treatment. Roussy and Clunet observed slight temporary improvement in two cases, a distinctly bad effect in two others, and no effect in a fifth case. They report a condition of parathyroid hyperplasia (whether primary or secondary not determined) in this disease. Oppenheim recommends the administration of doses corresponding to 0.05 gram of the fresh gland several times a day.

Favorable results have been reported from the use of parathyroid in eclampsia, epilepsy, and chorea—especially of adults (Garavini). It will be recalled that several clinicians have reported favorable effects from the use of *thyroid extract* in eclampsia, on the theory that this type of tetany is due to thyroid deficiency (Nicholson, Sturmer).

Morris reports injurious effects following prolonged administration of parathyroid gland by mouth. In a patient with *paralysis agitans*

the feeding produced disturbing mental symptoms and insomnia, but no improvement of the paralysis agitans.

METHOD OF ADMINISTRATION

Various commercial dry preparations have been put on the market. Berkeley recommends the use of glands prepared as follows: Freshly obtained ox glands are trimmed, pressed dry between folds of gauze, minced and rubbed up in a mortar with an excess of milk sugar, all the operations being carried out aseptically. One per cent. boric acid is added as a preservative and a trace of a volatile oil, usually peppermint. The preparation is administered in capsules, each corresponding to one-half grain of the fresh gland.

The administration both by the mouth and hypodermically of large doses of parathyroid to normal human beings had practically no effect (Esterbrook), but Morris reports serious deleterious effects in one case of paralysis agitans.

Summary

1. Parathyroid deficiency in man and experimental animals leads to chronic nervous hyperexcitability, occasional tetany, and some cachexia. Total loss of the parathyroids leads to death in from two to fifteen days in tetany or extreme cachexia. The primary disturbance following parathyroid ablation appears to be due to some derangement in metabolism leading to alkalosis, acidosis, and accumulation of toxic protein derivatives in the blood and urine.

2. All substances or therapeutic measures that temporarily reduce the excitability of the nervous system will diminish or prevent parathyroid tetany temporarily, but they cannot save the life of the patient or the experimental animal in total absence of the parathyroids.

3. No definite causal relation between parathyroid deficiency and the diseases of eclampsia, infantile tetany, gastro-intestinal tetany, paralysis agitans, etc., has so far been established. The reports on parathyroid organotherapy in these maladies are so conflicting and unsatisfactory that no reliance can be placed on the few favorable results recorded. Parathyroid organotherapy in these conditions is at present purely experimental and empirical.

4. The results to date on man and experimental animals indicate that true parathyroid tetany cannot be controlled, even temporarily, by giving parathyroid gland by mouth, or by transfusion of normal blood. The hypodermic or intramuscular administration of parathyroid extracts is of doubtful value, even as a temporary measure, and animal experiments show conclusively that such administration fails to prevent death in tetany or cachexia in the total absence of parathyroid. In light of our present

experimental and clinical experience, parathyroid transplantation is the most promising therapy in all types of parathyroid deficiency. The extremely conflicting results of parathyroid organotherapy, both in man and animals, are probably due to the frequency of accessory parathyroids, so that alleged complete parathyroidectomy is in many cases only partial parathyroidectomy, with temporary nervous hyperexcitability and tetany symptoms. According to the researches of Halsted and others such parathyroid remnants will undergo hypertrophy and may finally meet the entire need of the organism, in which case the animal or the patient recovers permanently. Any therapy of such temporary tetany conditions will be successful, by *post hoc* reasoning, although it has nothing to do with the recovery of the animal or the patient, except such measures as may temporarily check the hyperexcitability of the nervous tissue.

5. With the modern care in thyroid surgery cases of definite parathyroid deficiency in man become less frequent. Parathyroid organotherapy of other types of clinical tetany will contribute little or nothing to medical progress until further advances have been made in the physiology, pathology, and chemistry of the parathyroid glands.

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THYMUS

Physiology.—The thymus develops in the embryo from the epithelium of the third branchial pouch. Its origin is thus similar to that of the thyroids and the parathyroids. We have seen that accessory thyroids and parathyroids are frequently found embedded in the thymus tissue. The thymus is primarily an organ of fetal and pre-adolescent life, as in normal men and animals it undergoes involution at puberty, and is finally replaced by connective tissue, lymphoid tissue, and fat. But it is reported that the thymus of birds does not undergo involution at sexual maturity (Soli). Janson reports "accidental involution" of the thymus in starvation and malnutrition. The relative size of the thymus is greatest shortly after birth.

The thymus contains several types of cells. The outer or cortical portion of the gland is made up of lymphoid cells. According to Danschakoff these small cells of the thymus cortex differentiate into the various forms of leukocytes of the blood and lymph. The central portion, or medulla, is composed of a few lymphoid cells and the peculiar "corpuscles of Hassal," composed of nests of epithelial cells. The function of the Hassal's bodies is not known.

The specific rôle of the thymus is still very obscure, and Schäfer questions whether it should be classed with the endocrine glands. The organ is not necessary for life. The facts definitely established are: the involution of the organ at puberty, the delay of this involution by castration, and the apparent influence of the thymus on bone metabolism in early life.

Henderson states that early castration accelerates the growth of the

thymus and prolongs or delays involution. Involution of the thymus occurred especially rapidly in animals used for breeding purposes. On the other hand, Paton states that removal of the thymus in sexually immature animals led to a rapid growth of the testicles.

From the above experiments and observations it has been concluded that the thymus exerts an inhibitory action upon the development of the testes; and that the development of the testes has an accelerating effect upon the involution of the thymus. Paton concludes from more recent experiments that thymus and testes both exercise an influence on the growth of the sexually immature animal; the removal of both retards

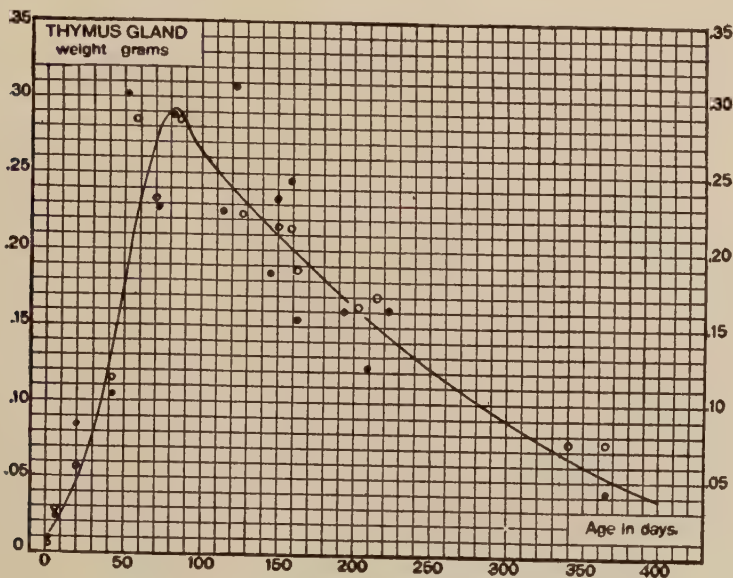


FIG. 7.—CHART SHOWING THE WEIGHT OF THE THYMUS OF THE ALBINO RAT ACCORDING TO AGE. The observed weights are represented by 229 males and 207 females. (Hatai.)

growth. This has not been established for the ovaries and thymus of the female. After removal of one the other can compensate for its loss, and in doing so may undergo a more rapid growth, or, in the case of the thymus, may persist for a longer period. Further evidence of a relation between the thymus and sex glands has been sought in the fact that the ovaries are sometimes enlarged in status lymphaticus (Bartel and Herrmann).

The relation of the thymus to growth was studied by Basch and others in young animals from which the thymus was removed. Such animals are said to show delayed growth and diminished intelligence. The changes in the bones were especially marked; these showed deficient ossification. Basch, and Paton also, reported that the peripheral nervous system showed an increased excitability, as determined by galvanic stimulation, and Paton

suggests that there is a close relation of the thymus and the parathyroid functions.

Klose, and Klose and Vogt state that if the thymus is removed from puppies about ten days after birth, there is a latent period of two to four weeks followed by a condition of adiposity for two to three months, then cachexia and a condition resembling idiocy, and death in "thymic coma" after three to fourteen months. They say that extirpation of the thymus in infants is followed by similar results. They consider the gland to be a vital organ in early life. They also state that the bones of animals deprived of the thymus have only about half the normal amount of calcium. They consider the bone and other changes to be due to acid intoxication, and that one of the functions of the thymus is to inhibit the formation of or to neutralize an excessive formation of acids, probably nucleic acid. The administration of thymus to dogs deprived of these glands was said to greatly aggravate the effects of thymectomy.

The thymus is very often found persistent or enlarged in cases of Graves' disease, especially in the severer forms. Capelle and Bayer believe that an internal secretion of the thymus aggravates the symptoms, especially the cardiac symptoms of this disease. They report improvement from thymectomy. Bircher stated that the implantation into animals of a pathological thymus caused symptoms of Graves' disease, such as tachycardia and tremors.

But Nordmann states the removal of the thymus shortly after birth in dogs has no effect on growth or other physical conditions. Morgulis and Gies report that the calcium content of the bones and teeth of thymectomized rats remained the same as in the normal controls; hence they contend that the thymus has no definite or necessary influence on bone growth.

The experimental results from thymectomy are therefore very contradictory, probably owing to the difficulty of complete removal of the organ. Koenig reports a resection of the thymus in a nine months old child followed by severe and prolonged rachitis. There is no evidence, however, that the thymus resection was the cause of the rachitis. Rachitis has also been ascribed to the removal of the carotid gland (Betke).

Rachford believes that the thymus produces an internal secretion affecting nutritional processes, especially in fetal life and early childhood; he believes that status lymphaticus is due to an excessive activity of the thymus, as Graves' disease is believed to be due to an excessive activity of the thyroid. Friedländer stated that exposure of the thymus to Roentgen rays causes diminution in the size of the spleen and lymph nodes in status lymphaticus. Nordmann thinks that some cases of toxic goiter are due to abnormal functioning (hyperplasia) of the thymus. Feeding thymus to young rats delays sexual maturity, especially in the male, with marked degeneration of the testes.

Gudernatsch, and Laufberger found that feeding thymus accelerates growth of frog tadpoles. Shimizu claims to have produced a thymotoxic serum (thymolysis), the injection of which produces the same results as thymectomy. Ott and Scott report that thymus extracts have a lactagogue action. This is erroneous.

THERAPEUTIC USES OF THE THYMUS

Thymus has been administered in many diseases (gout, goiter, marasmus, infantilism, rheumatism, acromegaly, Addison's disease, etc.). Mikulicz reports favorable results from thymus feeding in simple and toxic goiter. Uncertain or negative results from the administration of thymus in goiter (simple and toxic) were reported by Mackenzie, White, Parker, and many others. There are no data on the effects of thymus feeding on experimental hypothyroidism, where all conditions can be controlled.

Especial emphasis has been laid upon its value in rickets and, recently, in metabolic osteo-arthritis: Nathan administered it in doses of from two to four "5-grain" tablets (each tablet apparently containing dry gland equivalent to five grains of the fresh gland) three times a day for long periods. The 186 cases treated practically all improved "When the thymus is conscientiously taken for a long time, *and the patient is otherwise judiciously handled*, marked improvement, if not a perfect cure, can always be expected." "The otherwise judicious handling" of the patients was probably more important in the recoveries than the thymus feeding.

Favorable results (delayed growth and relief of pain) have been reported from its use in carcinoma. It has been administered by hypodermic injection of extracts and by the mouth. Gwyer administered it by the mouth in doses of from 30 to 120 grains (2.0 to 8.0) of the dried powder three or four times a day in goiter, arteriosclerosis, rheumatoid arthritis, hemorrhoids, cystic tumor of breast, pulmonary tuberculosis, and cancer. Takaki used far smaller doses and stated that gastric disturbances frequently occurred during its use. Haneborg reports good results from thymus feeding in chorea.

Summary

1. There is, at present, no rational or useful organotherapy of the thymus. The empirical and experimental thymus therapy of the past has not added to medical knowledge or contributed to the control of disease, as none of the maladies in which thymus treatment has been tried have been shown to be related to thymic hypo- or dysfunction. So far as thymus feeding produces any effects at all, either in health or disease, it is probably due to the high nucleoprotein content of this gland. No specific

thymus secretion or hormone is so far indicated by experimental and clinical work.

2. The possible relation of the thymus to bone metabolism and to the thyroid should be cleared up by further well controlled experiments.

3. In view of the apparent antagonism of the thymus to the testes, thymus therapy might prove useful in cases of sexual precocity and hypergenitalism due to gonad hyperplasia. It might also be possible to induce involution in cases of "persistent thymus," or thymus hyperplasia by gonad therapy. But the Roentgen rays have proved very efficient in such cases.

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THE HYPOPHYSIS

Within very recent years our knowledge of the functions of the hypophysis and of its derangements has been greatly increased. Nevertheless, *it is not yet possible to speak of a rational or definitely established organo-therapeutics in connection with this gland.* Our knowledge of conditions of deficient functioning of the hypophysis in which alone a true organo-therapeutics would be indicated, is still very imperfect, and the gland has not yet been used extensively in these. On the other hand, recent studies have shown that a part of the hypophysis contains a substance which, like epinephrin and alkaloids of vegetable origin, has marked pharmacodynamic effects, and which has proved to be of therapeutic value, not as an organo-therapeutic agent but in the way that epinephrin and other drugs are of value in the control of physiological processes.

STRUCTURE OF THE HYPOPHYSIS

Anatomical, histological and physiological researches have shown that the hypophysis is a very complex organ both as to structure and function. The anterior lobe (the *glándula pituitaria* proper) develops from a diverticulum of the pharyngeal epithelium, and is therefore of ectodermal origin. The posterior lobe (*pars nervosa*, or true hypophysis) is a diverticulum from the neural tube (floor of the third ventricle). In the adult

this lobe appears to consist of neuroglia cells together with a few nerve cells, and, in some species, of cells and colloid derived from the pars intermedia. The *pars intermedia* is made up of modified anterior lobe cells in immediate contact with the posterior lobe. In some animals these pars intermedia cells penetrate for some distance into the posterior lobe.

The anterior lobe, true to its epithelial origin, has clearly a glandular structure. But the cells making up the organ are not of uniform struc-

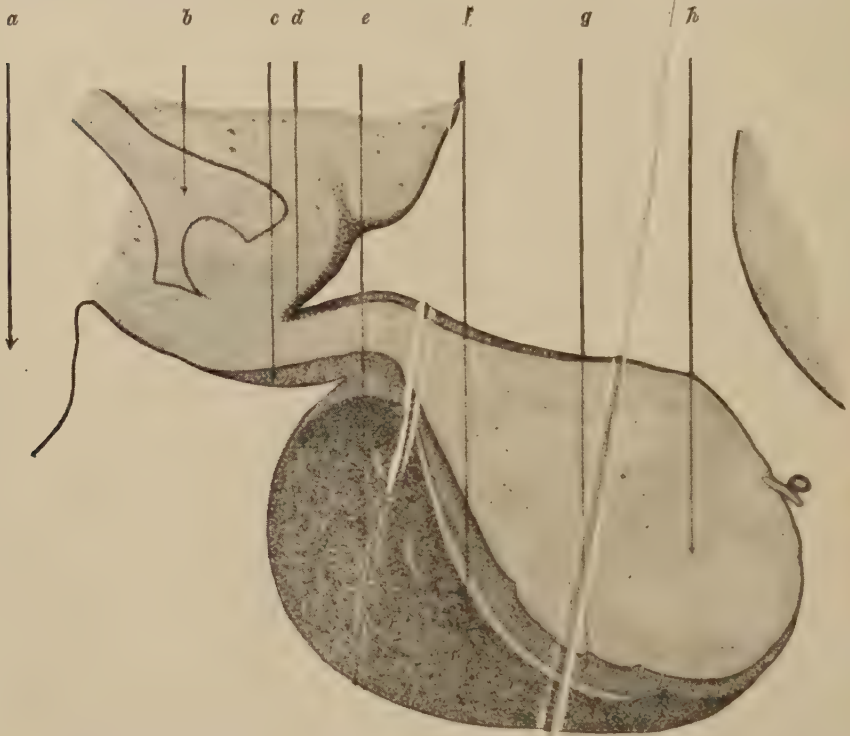


FIG. 8.—MESIAL SAGITTAL SECTION THROUGH THE PITUITARY BODY OF AN ADULT MONKEY (SEMI-DIAGRAMMATIC). (Herring.)

a, optic chiasma; b, third ventricle (infundibulum); c, d, extension of pars intermedia round neck of pituitary; e, pars anterior seu glandularis; f, intraglandular cleft; g, pars intermedia; h, pars nervosa.

ture and staining reactions. The cells are usually classified on the basis of their reactions to stains as (I) chromophile and (II) chromophobe. The first group is again subdivided into acidophile and basophile cells.

Whether these three groups of cells in the anterior lobe represent three distinct and separate lines of function or only different physiological states of one type of function is still an open question. The chromophile cells contain what appear to be true secretion granules, and these are usually most abundant in the region of the cell adjacent to the lymph spaces and the blood capillaries.

The hypophysis thus resembles the adrenal glands in origin. The physiological significance of this juxtaposition or fusion of nervous and epithelial structures into one gland remains unknown. Gaskell has advanced the theory that the hypophysis represents the vestigial remnant of the esophagus of our vertebrate ancestors, in whom the alimentary tract is supposed to have been placed dorsal to the spinal cord. But the serious effects following disease or of the removal of the hypophysis go to show that it is not vestigial in function, whatever be the significance of its peculiar origin and composition.

The histological picture of the hypophysis, especially the anterior lobe, is by no means constant throughout life. There appears to be an increase in the chromophile cells at puberty, and a gradual diminution of them after the fortieth year of life, indicating an adjustment of the organ to metabolic rate and possibly to the sex life.

Gemelli, also Cushing and Goetsch, report that in hibernating animals during hibernation, the hypophysis decreases in size, and the cells of the anterior lobe lose their characteristic staining reactions to acid and basic dyes. At the end of hibernation the gland again enlarges, cell division is in evidence and the cells regain their normal staining reactions. On the basis of these findings they accept the theory of Salmon that the depression of the activity of the hypophysis is the primary factor in causing hibernation, especially since partial hypophysectomy induces depression, obesity, and somnolence in non-hibernation animals. It must be noted, however, that completely or nearly completely hypophysectomized dogs of Aschner, some of which lived over a year, did not hibernate. Their appearance did not even suggest the condition of semi-hibernating animals. The more recent experiments of Mann failed to confirm the hibernation changes in the hypophysis described by Gemelli, and by Cushing and Goetsch. "There is no basis for the theory ascribing the phenomena of hibernation to lack of function of any or of all the endocrine glands."

According to Fenger, the formation of solid colloid in the pituitary gland does not occur during the growth period, but it is a phenomena of adult life. The solid colloidal material in the clefts of pars intermedia is insoluble in all ordinary solvents and is physiologically inert.

The hypophysis has a very rich blood supply. According to Dandy and Goetsch, the anterior lobe receives the blood supply from eighteen or twenty small arteries from the various components of the circle of Willis. These vessels immediately break up into numerous large sinusoidal channels, in apposition with the gland cells and lined only by endothelium. "Hence there are no veins or arteries proper in the anterior lobe substance." The pars intermedia derives its blood supply from the vessels of the stalk, from the posterior lobe, and from the adjacent brain. The posterior lobe is supplied by an artery derived from the internal carotid.

A clear knowledge of the hypophyseal circulation is necessary for in-

terpretation of the results of surgical interference (experimental and clinical) with this organ. From the sympathetic carotid plexus nerve fibers pass to the hypophysis, particularly the anterior lobe (Dandy). It is not known whether these nerves have vasomotor, secretory, or sensory function.

On the assumption that the colloid of the posterior lobe constitutes the internal secretion of this part of the gland and the relation of these colloid masses to the cells and fibrous tissue, Herring has advanced the view that this secretion is normally discharged into the cerebrospinal fluid of the third ventricle. This theory is accepted by Cushing and Goetsch, and by Cow, and they report the presence in the cerebrospinal fluid of a pressure substance identical in character with pituitrin. But the results of Cushing have not been confirmed (Carlson and Martin). There is no demonstrable trace of pituitrin in the cerebrospinal fluid of the normal dog. Wulzen supports the theory of a direct absorption of the pituitary secretion by the lymph and blood vessels. Herring himself has shown that in some of the animals there is no passage of colloid into the hypophyseal stalk. And as for the view that the colloid constitutes the important secretion, tests on the colloid found in the hypophyseal cleft show it to be physiologically inert.

Accessory Hypophysis.—Small nodes of glandular tissue apparently identical with the anterior lobe are present in many animals, including man, as the so-called pharyngeal hypophysis. If this pharyngeal hypophysis actually represents part of the original connection of the intracranial hypophysis with the pharyngeal ectoderm, we would expect it to exhibit evidence of functional changes synchronously with the anterior lobe. Unfortunately but little attention has so far been given to this by clinical and experimental workers.

Nodules of glandular tissue inside the cranial cavity in the neighborhood of the hypophysis proper have been described by Dandy and Goetsch under the name *parahypophysis*.

FUNCTION OF THE HYPOPHYSIS

Historical.—The beginning of accurate knowledge of the rôle of the hypophysis dates back less than a generation, and the slow progress of our knowledge of this gland is partly due to its inaccessibility and intimate association with the base of the brain. Galen thought that the hypophysis served to filter or secrete mucus (pituitam) from the brain into the nasal passages, hence the name *pituitary gland*. Then we have the equally fanciful view of Piccolhomini and of Descartes that the gland is the seat of the soul, or acts as a plug to prevent the escape of life principle from the third ventricle. Others looked upon the gland as an ordinary lymph node, as similar in function to the choroid plexus, secreting or changing the cerebrospinal fluid, or as ordinary nervous tissue.

The most important steps in the development of the knowledge of the functions of the hypophysis were the following: The observation (beginning with Rogowitsch, 1889) that extirpation of the thyroid, the gonads, or the pancreas leads to a hypertrophy of the hypophysis; the discovery of Marie (1886) of an association between acromegaly and anatomical changes in the hypophysis; the discovery (beginning with Oliver and Schäfer, 1895) that extracts of the gland have marked effects upon the blood pressure, the heart, and the smooth musculature of the body in general, especially the uterus; the discovery of Frölich (1901) of a relation between the hypophysis and the condition known as *dystrophia adiposogenitalis*; the demonstration (by several investigators, but especially by Paulesco, 1907, Cushing, 1909, and Aschner, 1912) that the total or nearly total extirpation of the gland is followed by death or by very characteristic effects upon growth and development; the discovery of the relation of the hypophysis to renal activity (beginning with Schäfer, 1906) and to diabetes insipidus; the studies on the influence of feeding, hypophysis, on general growth and on development of the gonads (Schäfer, 1909, Goetsch, 1916, Robertson, 1916).

A more detailed study of some of these investigations will serve to show the present state of knowledge of the function of this gland, and the conditions in which the gland or its extracts may be expected to be of therapeutic value.

Function of the Posterior Lobe and the Pars Intermedia.—These two parts of the gland must at present be considered together, because though differing in structure and origin, they are anatomically so closely interwoven that they cannot be separated for experimental purposes.

ACTION OF THE EXTRACT.—Oliver and Schäfer found that extracts of the entire gland raised the blood pressure. Howell subsequently showed that these effects were due entirely to the posterior lobe. Schäfer and Herring, Herring, Cushing and Goetsch, Lewis, Miller and Matthews, have found that the active principle seems to be formed in the pars intermedia, from which it passes into the posterior lobe. It is also possible that the presence of the pressor substance in the posterior lobe is due to the pars intermedia cells distributed among the neuroglia cells and fibers. In



FIG. 9.—TWELVE-MONTHS'-OLD HYPOPHYSECTOMISED DOG (LEFT) AND CONTROL OF SAME LITTER (RIGHT). (Aschner.) The operation was performed at eight weeks.

adult humans there appears to be no true *pars intermedia*, yet the posterior lobe contains the pressor substances.

The most marked physiological action of extracts of the posterior lobe is to cause a constriction of smooth muscle. The constriction of the arteries following the administration of such extracts leads to a marked, and, as compared with the effect of epinephrin, long-continued, rise of blood pressure. The extracts also cause dilatation of the frog's pupil, strong contractions of the uterus and of the alimentary tract.

There is thus some resemblance between the effects of extracts of the pituitary and of the adrenal medulla; this is, however, only superficial. The effect of epinephrin upon organs containing smooth muscle is gen-

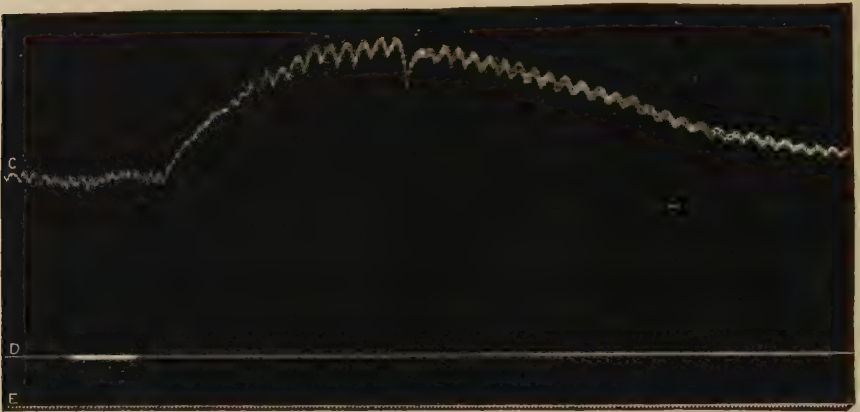


FIG. 10.—TRACING SHOWING THE EFFECT OF INTRAVENOUS INJECTION OF EXTRACT OF THE POSTERIOR LOBE OF THE HYPOPHYSIS ON THE BLOOD PRESSURE. (Schäfer.)

erally the same as that of the stimulation of the sympathetic nerves supplying these organs; when the sympathetic causes inhibition instead of contraction, epinephrin does the same. The effects of pituitary extracts are entirely independent of the sympathetic nerves; they are exerted directly upon the muscle cells (Dale). The action of pituitary extract is more nearly like that of the digitalis series, but the effect on smooth muscle is much greater than on the heart muscle. Hence, the effects of the two drugs are in many instances different. Thus the pituitary causes marked constriction of the coronary and pulmonary vessels; epinephrin has but little effect upon these. Pituitary extract always causes marked contraction of the uterus, whether this is pregnant or at rest; the effect of epinephrin depends upon the sympathetic innervation, and so, under some circumstances, causes a relaxation. Epinephrin stimulates the endings of the sympathetic nerves of the heart, causing an acceleration and augmentation of the heart beat; pituitary extract causes a slowing and at first a strengthening of the beat, but this soon gives place to a weakening. The

latter effect is probably due in part to the constriction of the coronaries; this is antagonized in the intact animal by the rise of blood pressure, so that the secondary weakening of the beat is not usually observed.

Howell made the interesting observation that a second injection within one-half to one hour does not cause a second rise of blood pressure; it may even cause a fall. Later a rise again is observed. This observation is of importance in connection with the therapeutic use of the extract. It is not a true immunity, according to Dale, but small doses can be injected repeatedly at intervals of ten or fifteen minutes without significant failure

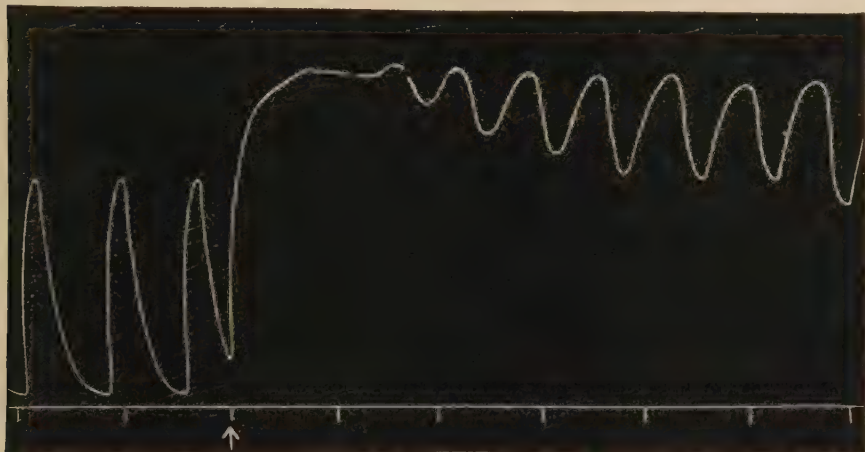


FIG. 11.—TRACING SHOWING THE ACTION ON AN ISOLATED CORNU OF RAT'S UTERUS SUSPENDED IN LOCKE'S SOLUTION OF THE ADDITION OF EXTRACT OF POSTERIOR LOBE OF OX PITUITARY TO THE SOLUTION. (M. Itagaki.)

of their pressure effect (Hoskins and McPeck). The active principle is excreted in the urine.

The rise in blood pressure following injection of posterior lobe extract takes place after removal of the adrenals, and is therefore not a secondary effect due to increased secretion of epinephrin.

V. Frankl-Hochwart and Fröhlich found an increased irritability of the autonomic motor nerves of the bladder to faradic stimulation. Similarly, the irritability of the hypogastric nerves to the uterus was much increased. These effects were produced only by the first injection of the extract.

Magnus and Schäfer, and Schäfer and Herring reported that the intravenous, subcutaneous, or intraperitoneal injection of extracts of the posterior lobe caused marked and long continued diuresis and dilatation of the kidneys. According to the same authors, administration by the mouth also increased the amount of urine secreted, both in animals and in man.

There has been considerable discussion as to whether this diuresis is

due to a direct action upon the cells of the kidney or is brought about indirectly through changes in the circulation. Schäfer and Herring, and Hoskins and Means support the view that the action is primarily on the kidney cells directly, and only secondarily aided by the changes in the circulation, while Houghton and Merrill, and King, and Stoland conclude that it is purely a vascular phenomena, the pituitrin diuresis running parallel with the vasodilatation in the kidneys.

The statement of Schäfer that the administration of posterior lobe extract by mouth induces diuresis has not been substantiated by recent workers. In fact Orlandi, Konschegg, Hoppe-Seyler, Fry, Matzfeldt, and others report that feeding, but especially hypodermic injection, of posterior lobe extract decreases the urine volume both in normal persons and in various conditions of polyuria, such as diabetes insipidus, without influencing the total solids excreted. This would seem to indicate that so far as the posterior lobe of the hypophysis is related to diabetes insipidus, it is lack of the secretion rather than the excess of it that leads to the polyuria. When the extract is given by mouth or hypodermically, the absorption is too slow to induce marked vascular changes, and hence there does not appear the temporary diuresis seen on intravenous injection. How posterior lobe feeding checks diuresis and reduces the urine volume in normal persons and in polyuria is still an open question.

Borchardt, Goetsch, Cushing, and Jacobson found that injection of posterior lobe extract may induce hyperglycemia and glycosuria, analogous to the action of epinephrin. It is not yet known whether the temporary glycosuria obtained by some observers is secondary to the disturbances in the circulation, or is an index of a primary and special relation of the posterior lobe to carbohydrate metabolism. Falta, Franchini, Guadri, Masi, and others maintain that the administration of posterior lobe extract does not induce hyperglycemia or glycosuria. Intravenous injection of extracts of fresh pituitary gland, the anterior or the posterior lobes, or the implantation of the entire fresh gland into the animal does not produce glycosuria in the dog. This is at least true of the quantity of the hypophysis represented by 2-10 glands of the dog (Carlson and Martin).

The Action of Posterior Lobe Extract on the Mammary Gland.—In 1910 it was reported by Ott and Scott, and subsequently confirmed by Schäfer and Mackenzie, Maxwell and Rothera, and a number of other observers, that injection of posterior lobe extract into lactating animals and lactating women causes a temporary flow of milk from the nipple. This was first thought to be a true "lactagogue" action, and hence of great practical importance in medicine. But Ott and Scott reported a similar "lactagogue" action from the injection of thymus, pineal gland, and corpus luteum extract, and it was soon discovered that on continued administration of posterior lobe extract there is no increase in the total milk yield either in experimental animals or in women. And it has now been demonstrated

(by Gaines and others) that the apparent lactagogue action of hypophysis extract is due to the contraction of the smooth muscle in the duct spleen forcing out any milk already formed in the gland, and not a stimulating action on the milk producing cells. It is another instance of the action of posterior lobe substance on smooth muscle and is of no practical importance in pediatrics and gynecology.

Weed and Cushing recently reported that extracts of the posterior lobe of the hypophysis increase the rate of production of cerebrospinal fluid (choroidorrhea) by stimulating the secretory activity of the choroid plexus. But Beeht has shown that the apparent increase in the cerebrospinal fluid after such injections is due to circulatory and respiratory changes following the pituitrin injection, and not to an increased secretory activity. Cow reports that extracts of duodenal mucous membrane stimulate the posterior lobe to increased secretion. His experiments are not convincing.

Posterior lobe extract, intravenously injected, has a direct action on the respiratory center, causing usually an increase in depth of the respiratory movements, followed by shallow and slow respiration (Nice, Rock and Courtright). It decreases the rate of secretion of the saliva (Stoland and Lommen).

Continued daily injections of posterior lobe extract are very deleterious, leading to emaciation, depression, fever, tissue changes—especially in the liver, vascular disturbances, etc. Harvey reports sclerotic changes in the coronary vessels after repeated injection of pituitary extract. This is of great practical importance. It is evident that the various posterior lobe extracts, so far prepared, do not represent the normal secretion or substance passed into the blood by the gland, or else these substances are contaminated by injurious split products of the cell constituents.

The specific pressor substance in the posterior lobe and pars intermedia is in evidence in early fetal life; in cattle it can be demonstrated at the eighth week of gestation (McCord). In the pig fetus, only 175 mm. in length, the pressor substance is very abundant (Lewis). If this substance represents an actual internal secretion, the gland is evidently functioning during intra-uterine development.

The active principle or principles of the posterior lobe have not been isolated, and little is known as to their chemistry. They are dialyzable, are not destroyed by boiling, and are soluble in water and ethyl alcohol (Fenger); they resist peptic but not tryptic digestion. They do not give

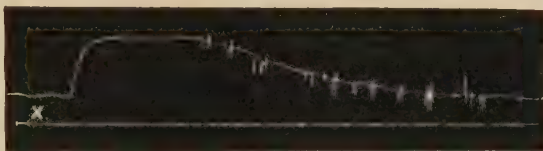


FIG. 12.—TRACING SHOWING THE CONTRACTION OF MUSCULATURE OF THE MAMMARY GLAND DUCT SYSTEM OF THE GOAT ON INTRAVENOUS INJECTION OF PITUITRIN. The air inflated gland is connected with manometer by cannula in teat. The air pressure in the gland before injection of pituitrin is 8 cm. chloroform. Time, 10 seconds. (Gaines.)

the color reactions characteristic of epinephrin, although they seem to give certain decomposition products analogous to those of this compound. Watanabe and Crawford failed to isolate epinephrin from the hypophysis. The colloid masses present in the adult's posterior lobe and in the pars intermedia are physiologically inert (Lewis, Miller, Matthews, Roth, Fenger). There is no iodine either in the anterior or the posterior lobe even after complete thyroidectomy (Wells, Simpson and Hunter). Relatively large amounts of calcium and phosphorus are present, besides traces of arsenic and bromine (Biedl); choline, guanine, and histidine have been reported (England and Kutscher, Aldrich). Crystalline substances showing some of the characteristic activities of posterior lobe extract have been isolated by Aldrich, Housay, and especially by Fühner; the latter investigator was able to isolate four crystalline substances exhibiting physiological activity. These were named collectively, by Fühner, *hypophysin*.

The commercial preparation, *pituitrin*, is an extract of the posterior lobe. One c.c. is said to correspond to 0.1 gram of the fresh or to 0.01 gram of the dried gland. "Pituitary liquid" is said to be a 20 per cent. extract of the fresh gland.

Standardization of Posterior Lobe Extracts.—Roth (1914) found that the various commercial preparations of the posterior lobe on the market varied greatly in physiological activity, some being fifteen times stronger than others. This is a very serious situation, in view of the increased use of this extract, especially in obstetrical practice, and because of the serious consequences (such as rupture of the uterus, etc.) that may follow the administration of too large a dose. In view of the fact that there is no seasonal variation in the activity of the posterior lobe, and little or no difference in the activity of the gland from different species of animals (cattle, hogs), the actual variations in the strength of preparations must be due to faulty processes of manufacture. It evidently does not suffice to state the strength of the preparation in terms of the percentage of fresh or dried gland present. Roth has demonstrated a practical method of standardization by comparing the extract (using guinea pig uterus as a test object) with a definite dilution of B-aminazolyethylamin hydrochloride. This substance can be prepared in chemical purity and has the same, only very much stronger, action on the uterus. An arbitrary standard of activity, making 1-10,000 dilution equal in activity to 1-20,000,000 dilution of the standard, is suggested.

It is obvious that such standardization of posterior lobe extracts for clinical uses would make the substance safer, and the results obtained from its administration more easily interpreted.

Feeding Experiments with Posterior Lobe.—These have so far thrown little or no light on the physiology or possible therapeutic use of the organ. Caselli, Sandri, and Goetsch report retardation of growth in young animals on continued feeding. Aldrich, Lewis and Miller noted no effect on

growth or health condition of the animals fed. Behrenroth obtained indications of increased rate of maturation of the gonads. Goetsch states that feeding the dried powdered posterior lobe extract to young rats in daily doses of 0.1 gram causes failure to gain in weight, increased peristalsis, mild enteritis, and certain nervous manifestations such as muscular tremors and weakness of the hind limbs. These effects are not produced by smaller doses (0.05 gr. per day). These smaller doses have no effect on growth, but seem to retard the development of the sex glands. A dose of 0.05 grain dried pituitary per day given to young rats weighing 25-50 grams is equivalent to a daily dose of 150-300 gr. dried gland in a person weighing 60 K.—a quantity far in excess of the total daily protein requirement of the individual. It would thus seem that these experiments are far outside the range of organotherapeutic possibilities for man. Feeding experiments must be made with smaller doses.

Function of the Anterior Lobe.—Most of our knowledge of the physiological importance of the anterior lobe has been secured by the method of extirpation, feeding the gland, transplantation, direct stimulation, and from conditions of diseases of the organ.

The Growth Controlling Principle of the Anterior Lobe—Tethelin.—Apart from the fact that extracts of the anterior lobe, like tissue extracts in general, on intravenous injection cause a temporary lowering of the blood pressure (Hamburger), nothing of importance has been gained by this line of study of the anterior lobe. Robertson has recently isolated an alcohol soluble substance, or a mixture of substances, from the anterior lobe, which, according to him, has the same stimulating action on growth as the entire gland, and hence named by him *tethelin*. It contains 1.4 per cent. phosphorus, and nitrogen in proportion of four atoms for every atom of phosphorus, some of the nitrogen being present in amino groups. It probably contains an iminazoly group, and to this extent may be regarded as related to the physiologically active substance of the posterior lobe. But tethelin does not possess the characteristic physiological activity of the posterior lobe extract, for large doses given intravenously have only a slight depressor action on the blood pressure, and practically no action on the heart, the uterus, or the musculature of the alimentary tract. If Robertson's results are confirmed the complete chemical isolation of tethelin will undoubtedly be of great clinical importance.

Extirpation of the Anterior Lobe.—The literature on the effects of partial and complete removal of the hypophysis since the first paper by Horsely (1886) to the extensive work of Aschner (1912) is as extensive as it is contradictory. Part of the conflicting results are due to the difficulties of the operation (extensive hemorrhage, injury to the brain, etc.). There is no doubt that removal of the gland by the buccal route is, in the hands of skilled experimenters, attended with less brain injury than the cranial route of Paulesco and Cushing. The most instructive results are

those reported by Cushing and his co-workers, Sweet and Allen, Aschner, and by Smith. Their studies, viewed in the light of the entire literature, appear to warrant the following conclusions:

1. Cutting of the stalk of the infundibulum, or removal of as much of the posterior lobe and pars intermedia as is possible without too great injury to the anterior lobe has no marked effect on the animal, except possibly some tendency to adiposity.

2. Complete or nearly complete removal of the anterior lobe in the young animals leads to retardation of growth, especially of the skeleton, prevents maturation of the gonads, thus causing failure of development of the secondary sex characters; evident mental depression, sluggishness and somnolence; tendency to excessive obesity; a lowered rate of metabolism, and possibly some increase in the carbohydrate tolerance, hyperplasia of the thyroid, thymus, and the cortex of the adrenals; it shortens the span of life.

3. The anterior lobe is necessary for normal growth and development, but its removal is not fatal. The death of hypophysectomized animals, as reported by many workers, within two to five days of the operation, with symptoms of extreme depression, is probably due to hemorrhage and brain injuries. At any rate it does not appear to be due to the loss of the anterior lobe. Complete removal of the posterior lobe and the pars intermedia is more difficult without injury to the base of the brain.

4. In the adult animal complete or partial removal of the anterior lobe induces a temporary hyperglycemia and glycosuria, excessive deposition of fat, and progressive atrophy of the gonads and the sex characters, and various histological changes in the other endocrine glands.

These extirpation experiments clearly point to an essential rôle of the anterior lobe in growth and maintenance, probably of every organ in the body, but especially the bony tissues, the gonads and the brain.

Transplantation of the Hypophysis.—In the hands of most observers the transplanted hypophysis appears to be quickly absorbed without producing any definite effects on the animal. Exner reports a temporary increase in growth when several glands were transplanted into young rats. Cushing and his pupils state that symptoms of complete or partial hypophysectomy are delayed or diminished, at least for a time, by transplanting a part of the gland. The same author reports favorable results, at least temporarily, from transplantation of a child's hypophysis into the brain of a patient suffering from hypopituitarism due to an hypophyseal cyst. There is nothing in the literature to indicate that a transplanted hypophysis becomes permanently functional in the host. Nor has it as yet been possible to produce any of the symptoms of acromegaly by implanting excessive amounts of hypophysis into animals.

Direct Stimulation of the Hypophysis.—Weed, Cushing and Jacobson report that direct stimulation of the hypophysis, mechanical or electrical, induces a temporary glycosuria. This is said to occur even after section

of the splanchnic nerves or the spinal cord below the level of the phrenic nuclei, showing that it is not due to brain and splanchnic stimulation. Cushing interprets the results as due to an excessive liberation of posterior lobe secretion into the blood by the stimulation of the gland. Using more accurate methods, Keeton and Becht showed that while direct stimulation of the gland induces hyperglycemia and glycosuria, this does not occur in animals with section of the spinal cord or the splanchnic nerves—a fact which argues against the liberation of an hypophysis hormone which increases directly the glycogenolysis in the liver.

The question of the possibility of inducing excessive hypophysis activity by direct mechanical stimulation of the gland is of great practical importance in cases of head and brain injuries and brain tumors in man.

The Question of Secretory Nerves to the Hypophysis.—This question is as yet an open one, owing in part to the fact that we have no certain test of hypophyseal hyperactivity in crucial experimental stimulations lasting, at the most, a few hours. Weed, Cushing and Jacobson, and Shamoff reported that stimulation of the cervical sympathetic nerve, and especially the superior cervical ganglion in rabbits, induces glycosuria. This they interpret as due to the stimulation of secretory nerve fibers passing from the cervical sympathetic to the posterior lobe. Using more accurate methods, Rabens and Lifschitz failed to confirm Cushing's results. Nerves to the hypophysis are present in the carotid sympathetic plexus, but most of these fibers are said to pass to the anterior lobe. The question of direct secretory nerves to the hypophysis is of great practical importance, and should engage the attention of biologists and clinicians. For if secretory nerves are present we probably have variations in the activity of the hypophysis parallel with the various conditions of increased and decreased activity of the sympathetic nervous system.

The Effects of Feeding and of Injection of Anterior Lobe Extract.—Results of great significance have recently been reported by this method, although the literature as a whole is contradictory.

Cushing, Sandri, Aldrich, Grail, Wulzen and Maxwell, and Lewis and Miller, and others report impairment of growth or loss of weight on feeding or injection of anterior lobe substance. This may be due to excessive doses used. Schäfer, on the other hand, reports little or no effect on growth from anterior lobe administration. Robertson, working on mice, and feeding fresh anterior lobe (0.125 gr. per day) found that when the feeding is begun at the fourth week of life there is first a retardation and later on an acceleration of growth, so that the hypophysis-fed mice finally attain, and may even surpass, the size of the control animals. However, the pituitary-fed animals are on the whole smaller than the controls, although they weigh more and appear to be more compactly built. There is certainly nothing in the data presented by Robertson that indicates an approach to acromegaly in the pituitary-fed mice. Robertson also

found that feeding the substance *tethelin* (isolated from the anterior lobe) produced essentially the same effect as feeding the entire lobe tissue.

In another report Robertson and Burnett state that injection of an emulsion of the anterior lobe into tumors (carcinomata) in mice increases the rate of the tumor growth without increasing the tendency to metastases. Wulzen reports further that the growth of planarian worms is accelerated by a diet of anterior lobe and pars intermedia, provided the feeding is begun early in life. Any part of the hypophysis increases the rate of fission in these lowly forms. Robertson also states that hypodermic injection



FIG. 13.—A, SECTION THROUGH THE UTERUS OF CONTROL RAT. B, SECTION THROUGH THE UTERUS OF RAT OF SAME LITTER FED FOR 42 DAYS WITH PITUITARY GLAND (WHOLE GLAND), SHOWING ACCELERATED DEVELOPMENT OF THE UTERUS. (Goetsch.)

tions of tethelin stimulates the action of tissue repair, as expressed in the replacement of tissue lost during a preceding period of starvation or in the healing of granulating wounds.

The extensive studies of Goetsch on white rats seem to demonstrate that continued feeding of anterior lobe to young animals accelerates body growth and hastens sexual maturity, while similar feeding of posterior lobe retards both growth and sexual development. When the anterior lobe is fed to adult rats sexual activity, as indicated by the number of pregnancies, is augmented. Goetsch's work appears convincing but it seems difficult to reconcile his 100 per cent. positive results with the slight or even negative findings of other investigators. Robertson and Wulzen gives the impression that the anterior lobe feeding did exert some stimulating action on the sex function in these animals (mice, chickens).

According to Pearl and Surface injection of anterior lobe substance or extract into the peritoneal cavity of fowls does not activate the com-

pletely resting ovary. Feeding the same to egg-laying hens does not accelerate egg production. Feeding the anterior lobe substance to young pullets does not bring about an earlier activation of the ovary. Feeding anterior lobe substance or desiccated corpus luteum to young pullets *retards growth*, but has no effect on the rate of development of sexual maturity.

Clark, on the other hand, reports that feeding anterior lobe substance to hens increases egg production as well as the fecundity of the egg. This effect becomes evident after three or four days' feeding, and persists a few days after ceasing the feeding. Clark's experiments are criticized by Pidot.

The present state of the literature on pituitary feeding of normal experimental animals seems to admit of the following conclusions:

1. Feeding anterior lobe may slightly accelerate the growth of young animals, but there is no evidence that the final stature is greater than that of the control animals. Hence there is no evidence of experimental acromegaly or gigantism.

2. Anterior lobe feeding appears to accelerate sexual maturation in the young and stimulate sexual activity in the adult animal, while the posterior lobe has the opposite action. But more work is needed before this thesis is established. In view of the conflicting literature, we cannot refrain from expressing the fear that some authors may have reported what they thought they ought to have found, rather than impartial objective results. Hypogenitalism and retarded growth are so manifestly the results of impairment or destruction of the hypophysis, and hence the fact that hypophyseal organotherapy ought to produce the opposite results appears so reasonable as to lull scientific critique.

FUNCTIONAL DISORDERS OF THE HYPOPHYSIS—HYPERPITUITARISM

For some time after the discovery of a relation between acromegaly and the hypophysis there was much discussion as to whether the disease was due to a condition of hyperactivity, of hypoactivity, or of a perverted activity of the gland. The theory has also been advanced that the pituitary changes in acromegaly are secondary to the bone growths and the general disorders of the body. It is now generally held, though not proven, that the former is due to hyperplasia and increased activity of the anterior lobe—at least in the early stages of the disease. The primary pathological condition in acromegaly is usually one of simple hyperplasia (adenoma) of the anterior lobe—especially an increase in the number of chromophile cells (Lewis, Csepai, Kahlmeter and others). It frequently shows indications of malignancy. At the same time there seems to be at least a functional involvement of the posterior lobe. In late stages there may be an extensive degeneration of the gland; and this has an important bearing

upon the possible therapeutic use of the gland in acromegaly. The amelioration which may follow the removal of part of the hypophysis in acromegaly (Hochenegg) affords additional proof that the condition is one of hyperpituitarism. At the same time it must be admitted that the precise relation of hypophyseal activity to acromegaly and gigantism has not yet been established. Cognetto advances the following argument against the generally accepted hyperpituitary theory.

1. Cases of acromegaly have been observed without tumors of the hypophysis.

2. Adenomas composed entirely of chromophilic cells of the anterior lobe have been found associated with acromegaly.

3. Adenomas of the hypophysis composed entirely of chromophilic cells, but without acromegaly, have also been described.

Two sets of symptoms are caused by hypertrophy of the hypophysis: (1) those which appear to be due to the specific hyperactivity of the gland; and (2) those produced by the pressure of a tumor in this region. The specific effects of hyperactivity, which may throw some light upon the normal function of the gland, are marked and characteristic changes in the features and in the extremities, due partly to the growth of the soft tissues, partly to an enlargement of parts of the bones of the head, feet, and hands.

Keith has studied in detail the changes in the skull in acromegaly, and the manner in which they are induced. He concludes that an internal secretion of the hypophysis sensitizes tissues so that they respond to the natural stimuli of growth (mechanical activity and muscular movement) with increased energy. The enlargement of the extremities is due largely to connective tissue growth.

Among other symptoms of acromegaly are lassitude, muscle pains, apathy, and disturbances in sexual activity; there may be amenorrhea in women and frequently impotence in men, but excessive sexual activity may also be present. Vasomotor changes in the skin are frequent. Polyuria, with or without glycosuria, is common.

Borchard found glycosuria in 40.3 per cent. of 176 cases. In later stages, where the hyperactivity of the gland is being replaced by hypoactivity, there is, according to Goetsch, Cushing, and Jacobson, not only no glycosuria, but an increased tolerance for carbohydrates; but these authors consider both the glycosuria (lowered carbohydrate assimilation) and the subsequent increased carbohydrate tolerance to be due to hyper- and hypoactivity, respectively, of the posterior lobe.

The literature on the condition of metabolism in acromegaly is conflicting, but in the early stages there appears to be a definite retention of calcium, magnesium, and phosphorus (Bergheim, Stewart, and Hawk) probably in consequence of the new bone growth. Part of the contradictory results is probably due to the fact that only the early stages of the disease are associated with hyperactivity of the anterior lobe, and this is followed

later by destructive changes in the gland and hypopituitarism (Tamburini, Schäfer). Since pure hyperpituitarism (experimental hypophysectomy) is followed by a lowering of the rate of metabolism, we would expect an increased rate of metabolism in acromegaly, if it is due primarily to hyperactivity of the hypophysis.

The studies of acromegaly show that there is a close relationship between the hypophysis and growth, especially of connective tissue, cartilage, and bone, and also between this gland and the activity of the sex glands, thus supporting the experimental results on the hypophysis.

The relation between the hypophysis and growth has been further emphasized by studies on gigantism; in this condition also hyperplastic conditions of the hypophysis are almost invariably found. In many of these cases, however, other glands of internal secretion are so greatly involved that it is impossible to determine whether the changes in the hypophysis are primary or secondary. The other glands chiefly involved are the sex glands, which are markedly atrophic, and the thyroid. In certain cases of dwarfism, on the other hand, the anterior lobe of the hypophysis is said to be destroyed (Aschner).

It is interesting to note in this connection that favorable results in precocious gigantism have been reported from the administration of ovary (Maisonave, Hudovernig and Popevitz), and that the changes in the hypophysis in animals following castration may be partly prevented by the injection of testicular extracts (Fiehera). Hatai reports, however, that in the albino rat there is no hyperplasia of the hypophysis following spaying, while castration of the male rat induces the hyperplasia. Tandler suggests that the special growth features of eunuchism may be due to the hyperplasia of the thyroid that follows castration.

A condition of hyperpituitarism is believed to exist, as has already been indicated, after castration, which usually leads to some enlargement of the hypophysis, and also during pregnancy, when some of the functions of the ovaries are in abeyance. There are not only characteristic changes in the hypophysis during pregnancy (Marck, Mayer), as indicated by increase in size and by very definite histological changes, but certain general symptoms of pregnancy (enlargement of the hands, changes in the facies suggestive of acromegaly) are considered to be due to the hyperpituitarism.

Removal of the thyroid also leads to hypertrophy of the hypophysis (Rogowitsch, Livingston); the latter is also found in many cases of hyperthyroidism in man. Symptoms referable to the hypophysis have been reported after thyroidectomies.

FUNCTIONAL DISORDERS OF THE HYPOPHYSIS—HYPOPITUITARISM

The condition of hypopituitarism is of interest in connection with the organotherapeutic use of the hypophysis. This condition is known both clinically and experimentally.

Clinically, a condition of hypopituitarism is known in the disease *dystrophia adiposogenitalis*, first described by Fröhlich in 1901. In this condition there are usually symptoms of hypophyseal tumor or cysts of a destructive character, combined with obesity, a hypoplastic condition of the sex glands, and retarded growth or infantilism. Some of these symptoms—notably the obesity, occur also in the later stages of acromegaly.

The view that this condition is really due to a primary involvement (hypofunctioning) of the hypophysis is largely based upon recent experiments upon animals (Cushing, Aschner) in which the hypophysis was partially removed, as detailed above. Crowe, Cushing, and Homans found in such experiments adiposity, transitory polyuria and glycosuria, loss of hair, subnormal temperature, diminution of sexual activity, and atrophy of the testicles and ovaries; there was a reversion to the infantile type. Histological changes were apparent in the thyroid. These results have been confirmed by Biedl, Aschner, Livon, and others. When operations were performed upon young animals there was a marked retardation of growth and a retention of infantile characters. It is not possible to determine at present whether some of these effects are primary or are secondary to the changes in the sex glands.

Aschner found that dogs recovering from a (partial) hypophysectomy showed a diminished glycosuria reaction to epinephrin, and an increase in carbohydrate tolerance.

Cushing and his co-workers at first believed that the above results were due to removal of part of the anterior lobe; now they believe that some of them (the adiposity and increased carbohydrate tolerance) are chiefly due to removal or injury of the posterior lobe. They believe that there are many cases of hypopituitarism in man, due to obstructive agencies (tumors or hydrocephalus), the existence of which may be discovered by a determination of carbohydrate tolerance. This may be possible by using the more accurate method of measuring carbohydrate tolerance, recently described by Woodyatt.

Several cases have been reported in which the administration of extracts of the hypophysis has caused improvement in the condition of *dystrophia adiposogenitalis*—thus affording additional evidence that this condition is one of hypopituitarism.

It must be admitted, however, that it is not possible to state with certainty, in cases of clinical hypopituitarism, which symptoms are due to lack of anterior lobe, and which are due to lack of posterior lobe activity. The clearing up of this point is of great practical importance for the

organotherapy of the organ. When the cysts or neoplasms become sufficiently large, it is probable that the activity of the entire gland is depressed (pressure atrophy) irrespective of the part of the gland giving rise to the tumor. The difficulty in the way of hypophysis organotherapy is further increased by the fact that many of the clinical symptoms of hypopituitarism may arise from dystrophy of other glands of internal secretion. Thus impairment of growth and dwarfism and retardation of gonad maturation may be due to thyroid deficiency; sexual infantilism may be due to pri-

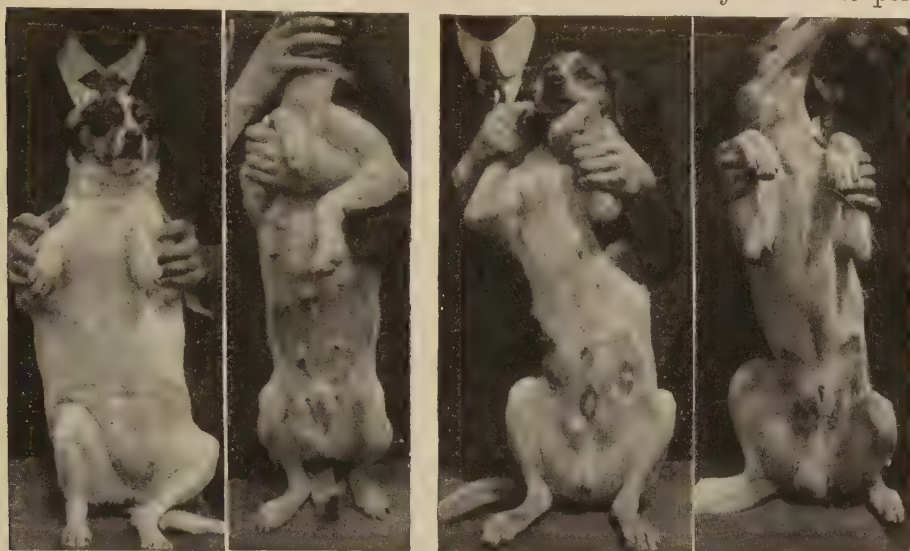


FIG. 14.—ADULT DOGS, MALE AND FEMALE, SOME MONTHS AFTER REMOVAL OF THE GREATER PART OF THE PITUITARY BODY. In each case a control of the same litter is shown on the right of the operated animal. The tendency to adiposity is marked in both sexes. (Cushing's "The Pituitary Body," pub. by J. B. Lippincott Co.)

mary impairment of the gonad; abnormalities in carbohydrate tolerance to disorders of pancreas and adrenals; and lowered metabolism and body temperature may be due to a great number of causes. Cushing, Falta, and others thus recognize a distinct group of cases with hypophysis involvement but showing at the same time signs of pluriglandular dystrophy. The organotherapy of this group is necessarily complicated, and is at present purely experimental.

Summary

Clinical observations and experiments show that the hypophysis is a structure essential to normal life, the removal of which may lead in a short time to death, the partial removal or disease of which leads to a condition of retarded growth or infantilism, to obesity, to atrophy of the sex glands, and other disturbances of nutrition. The hyperactivity of the anterior lobe (in acromegaly and gigantism) leads to accelerated and

abnormal growth, and ultimately to atrophy of the sex glands. It probably produces internal secretions passing directly into the blood. Nothing is known as to the nature of the action of this part of the hypophysis; why the gland is so immediately necessary to life is especially obscure.

The posterior lobe and pars intermedia contain a substance or substances having marked effects upon plain muscle, especially that of blood vessels and the uterus, and upon the kidney; while it thus has important pharmacodynamic actions, its rôle in the normal animal is obscure, since it is not certain that this substance is given off by the gland to the body fluids.

Especially marked are the relations between the hypophysis and certain other organs of internal secretion, the sex glands, the thyroid, and perhaps the suprarenals.

THERAPEUTIC USES OF THE HYPOPHYSIS

If the active principles of the anterior lobe are absorbed in active form from the alimentary tract, thus permitting administration *per os*, and if they are prepared in sufficient purity to permit of repeated intravenous, intramuscular or hypodermic injections without untoward symptoms, one might hope for favorable results from anterior lobe therapy in all diseases due, in whole or in part, to impaired functions of the hypophysis (hypophyseal dystrophy, infantilism, amenorrhea, impotency, or impaired growth traceable to the hypophysis).

The results of clinical use of the hypophyseal preparations have so far not come up to this expectation. In fact it has not yet been shown that the effects of partial or complete hypophysectomy in experimental animals can be essentially and permanently counteracted by hypophyseal organotherapy. The past failure may be due in part to using the entire gland, rather than the anterior lobe, as there is some evidence that posterior lobe substance counteracts the effects of the anterior lobe substance in some directions. It is also due in part to the use of posterior lobe substance, when anterior lobe material should have been tried. There is no disease so far definitely traced to deficiency of the posterior lobe.

On the basis of Benda's theory of acromegaly, administration of hypophysis (anterior lobe) is contra-indicated in the early stages of that disease, but it might be useful in the later stages of the disease when the gland appears to be gradually destroyed.

The use of posterior lobe extract as a uterine, intestinal, and vasomotor stimulant is not organotherapy, as uterine, intestinal, and vasomotor inertia are not definitely traceable to posterior lobe deficiency. This is drug action rather than organotherapy.

The literature shows that, besides the above, hypophysis therapy has

been tried with varying results in uterine inertia; incomplete abortion; threatened abortion; intestinal inertia; surgical shock; amenorrhea; menorrhagia; diabetes insipidus and polyuria; asthma; hemoptysis; vesicular inertia; insomnia; angina pectoris; to differentiate between true and false labor pains; osteomalacia; rachitis; rheumatic and gonorrheal arthritis; periostitis; tetany; epilepsy; dementia praecox; sterility, impotency; exophthalmic goiter; pneumonia; diphtheria; typhoid; hay fever; deficient milk secretion.

SPECIFIC ORGANOTHERAPEUTICS

The earliest attempts to use hypophysis in organotherapeutics were in connection with acromegaly. The results were very variable: many physicians obtained negative results, several reported distinctly favorable results, while a few reported injurious effects. A case described by Osborne may be cited as an example of the favorable results sometimes obtained: Under treatment with hypophysis (six to twelve grains daily), the headache, which had been continuous for two years, was rarely present, appetite improved, muscular weakness and nervous restlessness disappeared, and the patient was able to do her usual work, which she was not able to do before the use of the pituitary substance. The hypertrophy of the soft parts of the face, hands, and feet greatly diminished. On stopping the treatment the headaches and muscular weakness again developed, and the face and hands very noticeably increased in size. Similarly favorable results were reported by Kuh, in two of three cases, and by a number of other writers.

In addition to acromegaly, hypophysis has been administered to a number of cases of dystrophia adiposogenitalis (Levi and de Rothschild, Axenfeldt, Delille, Leman, Van Wort, Faltz, Cushing). In some cases improvement, as indicated by diminution of the adiposity and stimulation of the sex glands, was noted; in many cases, however, the results were negative. The administration of hypophysis has also been followed by improvement in cases of hypophyseal tumor—the symptoms of which could not be definitely classified, and in certain cases of obesity.

Cushing believes that there are many cases of hypoactivity of the pituitary, very often overlooked, in which the administration of hypophysis is indicated. He believes that an internal hydrocephalus, of whatever origin, is the most common source of moderate grades of this condition; a beginning adiposity and increased carbohydrate tolerance are very suggestive symptoms. The recent work of Goetsch, and of Robertson on feeding anterior lobe to animals appears to warrant continued and careful trial of anterior lobe preparations in hypophyseal dystrophies.

Therapeutic Uses of Extracts of the Posterior Lobe (PITUITRIN).—Extracts of the posterior lobe are used chiefly for their effects upon plain

muscle, especially that of the uterus and blood vessels. The nature of this action has already been discussed.

Many recent writers have reported very favorable results from the use of such extracts in uterine atony, and in postpartum and other forms of uterine hemorrhage. This use of pituitrin is now well established; several claim that it has distinct advantages over ergot in these cases. Foges and Hofstätter and Hofbauer lay especial emphasis upon the increased irritability of the uterus (sensitizing action of Frankl-Hochwart and Fröhlich), slight stimuli causing long continued contractions. Bab suggests that its effect on uterine hemorrhage may be due in part to its causing a diminution of the activity of the ovaries; the same idea has led him to employ it in cases of osteomalacia with, he states, much improvement in several cases. Macy, Whitbeck, and others report some improvement from pituitrin in gonorrheal and rheumatic arthritis.

Several writers have advocated the use of pituitary extracts to increase the blood pressure in shock and various infectious diseases (pneumonia, diphtheria, typhoid, etc.), claiming that it has the advantage over epinephrin of a much more lasting effect (Williams, Klotz, and others). Wray states that in postoperative shock the improvement in the circulation may last twelve to fifteen hours after the intramuscular injection of one c.c. of the 20 per cent. solution of the posterior lobe. Reese and others have reported good results from pituitary extract in asthma. This is probably an error except in the so-called "cardiac" asthma due to impaired circulation. In true bronchial asthma pituitrin not only has no effect, but may be harmful (Koessler).

Wiggers considers that it is the only drug which meets the indications for a hemostatic in pulmonary hemorrhage, since it raises the blood pressure from peripheral action (which constricts the bleeding points and at the same time prevents anemia of the brain), and causes a weakening of the heart, which prevents a rise of pressure in the pulmonary vessels.

Bell, Duffy, King, Stanley, and others recommended it in intestinal paresis after abdominal operations. It is said to act more powerfully on the paretic than on the normal intestine.

Klotz considers it especially valuable in peritonitis, where it not only increases the blood pressure, but stimulates peristalsis.

The vasoconstriction is not very marked when applied locally, but it has been recommended in hay fever, and as a local styptic in nose and throat operations.

Pal reports excellent results from the use of the extract in a case of severe tetany in a boy. Ludlum and Carson obtained good results from pituitary extracts in dementia precox.

The drug has been injected subcutaneously or intramuscularly in doses of 1 to 3 c.c. of the aqueous extract, 1 c.c. corresponding to 0.1 or 0.2 gram of the fresh gland (posterior lobe), or intravenously in doses of 1

to 2 c.c. diluted with 20 c.c. normal saline solution. There is danger of local necrosis when injections of strong solutions are made subcutaneously. It has also been given by the mouth in doses corresponding to 0.2 gram to 0.8 gram of the fresh gland, or 1 to 3 grains of the dried gland (posterior lobe).

The drug is contra-indicated in conditions of high blood pressure.

Although serious untoward results from its medicinal use do not seem to have been reported, except such accidents as uterine rupture from administration of pituitrin in labor before dilution of the os, it should be remembered that Harvey has produced sclerotic changes in the coronary vessels of animals; Crowe has seen loss of weight and marked changes in the liver from repeated injections; Thaon reports pathological changes in the kidney after prolonged use of large doses; and Franchini has observed intestinal ulceration and hemorrhage.

General Summary

While specific hypophyseal organotherapy is still in the experimental stage, our present knowledge appears to warrant the following recommendations:

1. Administration (*per os*) of anterior lobe in all cases of hypopituitarism.
2. Possible value of anterior lobe substance (*per os*) as a stimulant to general growth and repair processes.
3. The use of posterior lobe extract as a stimulant to smooth muscle (uterus, alimentary tract, cardiovascular system) and as an antidiuretic in diabetes insipidus. In the latter condition variable results have been observed, and care must be taken in the use of the preparation (See Diabetes Insipidus).
4. Physicians should insist (1) that posterior lobe extract is physiologically standardized by Roth's or similar methods; (2) and that anterior lobe extract be not prepared from the glands of old animals, as there are indications of gradual atrophy of the gland in old age.

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THE PINEAL BODY

According to comparative anatomy the pineal body represents a vestigial remnant of a median eye, but its histological structure, at least in youth, as well as some of the experimental physiology of the organ in birds and mammals indicate that it may be a gland of some importance, at least during pre-adolescence. Its physiological importance is, however, not yet clearly established.

The pineal body continues to grow until the age of seven to eight years, when atrophy or involution sets in; so that in the adult the pineal body is made up mostly of connective tissue cells and the so-called "brain sand." The average weight of the gland in man is 0.22 gram.

Jordan has noted the great abundance of the blood supply to the organ, but he does not think it is a gland of importance. The presence of sympathetic nerve fibers in the pineal body has also been asserted (Cajal).

The injections of extracts of the pineal gland have revealed no action of specific physiological importance—at least for the circulation (Jordan and Eyster).

McCord states that subcutaneous injections of sterile pineal gland (young calves) into young guinea-pigs three times weekly has a marked stimulating action on growth.

Extirpation of the Pineal Body.—According to Biedl, Exner and Boese, and Dandy, extirpation of the organ in adult dogs or in rabbits (young and adult) produces no demonstrable effects. Because of the location of the gland most of the operated animals die within twenty-four hours of hemorrhage, brain injury, and shock. But the few that survive the operation trauma are said to remain normal. Both Sarteschi and Foa report very different results from pinealectomy in young chicks, rabbits, and rats. According to Foa the operation has little or no effect in females, except a temporary retardation of growth. In the males the

extirpation of the gland leads to precocious sexual maturity. This acceleration of sexual maturity was also observed by Sarteschi in the operated male pups and rabbits. The most important and conclusive work in pineal gland extirpation is that recently reported by Dandy on young dogs. Dandy extirpated the pineal body in pups (male and female) ten days to three weeks old and observed their body growth, sex life, and mental behavior for eight to fifteen months after the operation. In no case did he find sexual precocity or indolence, adiposity or emaciation, somatic or mental precocity or retardation. Dandy concludes that "the pineal body is not essential to life and seems to have no influence on the animals' well being at any age."

FEEDING PINEAL GLAND EXTRACT

Dana and Berkeley, also McCord, state that feeding pineal glands to young animals (guinea-pigs) accelerates growth and hastens sexual maturity, both in males and females. There is no tendency to gigantism. The pineal-fed animals simply attain adult stature at an earlier period. According to McCord these effects are most striking when the pineal organ obtained from young animals (calves) is fed.

Dana and Berkeley also claim that feeding or injecting pineal gland to "backward" children improved their mentality, although growth of the body was not accelerated.

Tumors of the pineal body in the young have frequently been associated with acceleration of growth and pubertas precox, sometimes with cachexia, probably due to brain injuries.

The interpretation of the body changes in case of pineal tumors in the sense of hypo- or hyperactivity of the gland is very uncertain, especially in view of the contradictory results of animal experiments, Dana, Berkeley, and McCord finding that pineal feeding produces the identical results described by Foa and Sarteschi as following complete extirpation of the gland.

According to Biach and Hülles, castration and spaying lead to atrophy of the pineal body in cats. This is contrary to the results of castration previously reported by Sarteschi, and Schäfer remarks that in the cat the pineal body is normally very small.

There is, as yet, no rational or useful pineal gland organotherapy. The contradictory effects reported from work on animals and the uncertainty of the pineal deficiency in man must be cleared up before we are justified in trying pineal organotherapy in the clinics, even experimentally.

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THE PANCREAS

INTERNAL SECRETION FUNCTIONS

In 1889 von Mering and Minkowski discovered that complete extirpation of the pancreas in the dog produces fatal diabetes. This has been abundantly confirmed on all species of vertebrates so far investigated. The attempts of Pflüger and others to show that the diabetes following removal of the pancreas is due, not to the absence of the pancreas, but to injury to the duodenum and the nerves connecting the pancreas with the rest of the viscera, must be considered a failure. The original conclusion of von Mering and Minkowski is definitely established; the complete or nearly complete loss of the pancreas results in fatal diabetes. The more recent investigations of the condition of the pancreas in clinical diabetes (Ssobolew, Opie, Visentini, and others) have shown that in severe diabetes or in deaths in diabetes there is usually more or less degeneration of the pancreas, especially in the island tissue. The conclusion that the pancreas is absolutely essential to life and to carbohydrate metabolism is thus based both on experimental and clinical data. This conclusion is established beyond a doubt.

The part of the pancreas concerned in this function appears to be essentially the *islands of Langerhans*. This seems to be demonstrated by the following facts:

1. Loss of the external pancreatic secretion (by permanent fistula of the pancreatic ducts) does not induce diabetes.

2. Ligation of all the pancreatic ducts leads ultimately to complete degeneration of all the pancreas tissue, except the islands of Langerhans—at least in animals like the rabbit and guinea pig. Such animals with only islet tissue left do not develop diabetes unless these remnants of the pancreas are extirpated.

3. In clinical diabetes the pancreas lesions usually involve the islets. Despite these facts the view that the entire pancreas tissue is concerned

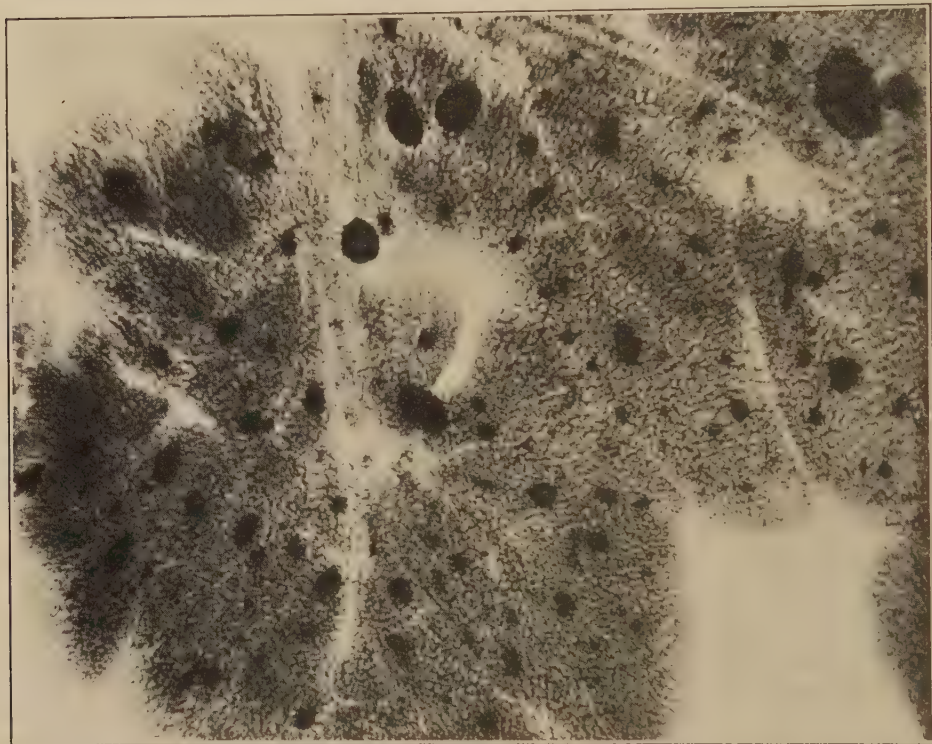


FIG. 15.—MICROPHOTOGRAPH ($\times 38$) OF A PORTION OF THE PANCREAS OF THE GUINEA PIG STAINED INTRA VITAM BY NEUTRAL RED, SHOWING THE NORMAL VARIATIONS OF THE SIZE AND FREQUENCY OF THE ISLANDS OF LANGERHANS—DARK AREAS. (Bensley.)

in the maintenance of the capacity of the tissues to oxidize the carbohydrates is still maintained by some clinicians and biologists (*cf.* Lombroso). This view finds its strongest support in the fact that human diabetes may reach a fatal issue while there still remains an abundance of apparently normal island tissue in the pancreas, as determined histologically. It is possible, however, that normal function is reduced or lost before anatomical or chemical degeneration of the cells reach such magnitude that they can be detected by the microscope. This theory of identity of function of the entire pancreas was also supported by the work of Dale, Vincent and Thomson, and others, which appeared to show

that the islets represented only stages of fatigue or rest of the ordinary pancreas tissue. Bensley, Laguesse, and others have shown that this is untenable. While the islets and the acini develop from the same embryological anlage (the cells of the ducts), when finally differentiated they show constant and specific structural and chemical characteristics, evidently indicating specificity of function; and there is no foundation for the view that the one tissue is or can be transformed into the other.

The Islands of Langerhans

The number and size of the islets vary greatly in different species, as well as in individuals of the same species. In some fishes they are macroscopic (5 x 14 mm.). In man the islets have been estimated to make up 1/25-1/100 part of the entire pancreas tissue, or a total of 2-3 grams. In a normal animal five-sixths of the total pancreas can be removed without inducing diabetes, so that the "factor of safety" is very great. The total number of islands in mammals appears to be fixed at or, rather, before birth (Bensley).

Lane and Bensley have shown that the island tissue is made up of two distinct types of cells, showing specific staining reactions, a less abundant alpha type, and a more numerous beta type. According to Homans it is the beta cells that show degeneration changes in clinical diabetes.

The islets develop from the undifferentiated duct cells and may or may not retain this original connection with the ducts, but in either case the blood supply of the islets is greater than to the rest of the pancreas tissue. In this respect the islets resemble the adrenals and the thyroids. In fact, blood sinuses similar to those of the adrenals have been described in the islets (DeWitt).

The islets are also abundantly supplied with nerve fibers (Gentes, Pensa, Laguesse). Groups of ganglion cells are also distributed in the body of the pancreas. The function of the nerves distributed to the islets is unknown. Some of them are undoubtedly vaso-motor nerves, but others form a network between or around the islet cells, which appears to indicate a secretory or reflex function.

EXPERIMENTAL PANCREATIC DIABETES

Extirpation of the whole or more than six-sevenths of the pancreas leads to fatal diabetes in all animals. In birds pancreatectomy leads to hyperglycemia, cachexia, and death, but there is said to be little or no glycosuria, because of the relative impermeability of the renal epithelium of birds to sugar. Following the fundamental discovery of pancreatic diabetes by v. Mering and Minkowski in 1889, a tremendous amount of

work had been done to elucidate the nature or mechanism of this diabetes (*cf.* Allen, 1914). The following facts are established:

1. Hyperglycemia and glycosuria appear within a few hours after pancreatectomy and, together with polyuria, polyphagia, and polydipsia, persist until shortly before death, even when no food is given. If the hyperglycemia of human or experimental diabetes is sufficiently marked the sugar appears in the saliva, gastric and pancreatic juice, and in the bile (Carlson and Ryan, Pearce).

2. The liver and the muscles become practically free from glycogen,

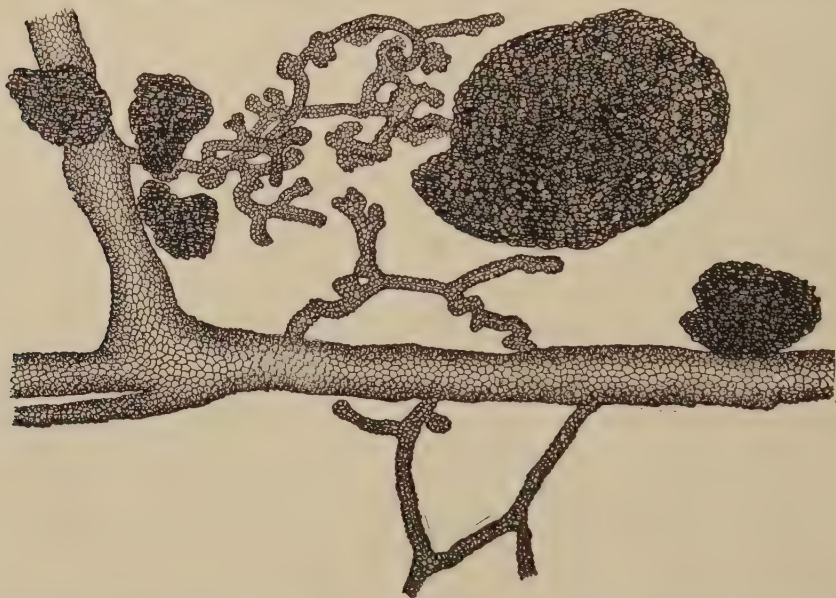


FIG. 16.—PANCREATIC DUCT WITH BRANCHES SHOWING THE HIGHLY BRANCHED TUBULES CONNECTED WITH THE DUCT AND WITH AN ISLET. INTRA VITAM STAINING WITH PYRONIN AND NEUTRAL RED. $\times 77$. (Bensley.)

but the essential factor is not the inability to store glycogen (alimentary glycosuria) but a *greatly diminished capacity, if not complete inability to oxidize the sugar*. The respiratory quotient is therefore low (Murlin and Kramer). Nishi states that perfusion of the liver of pancreatectomized turtles with Ringer's solution plus glucose leads to storage of glycogen in the liver cells.

3. There is marked polyphagia (Luckhardt) and a striking increase (15-20 per cent.) in the total metabolism per unit of body weight. Morehouse, Patterson, and Stephenson report that total pancreatectomy increases the total metabolism 15-20 per cent. There is no rise in the respiratory quotient after giving glucose or fructose. The increased excretion of the acetone bodies parallels the increase in the D: N ratio.

4. There is usually some acidosis and ketonuria, but these symptoms

of diabetes are, at least in the dog, not as marked as in clinical diabetes, and the completely pancreatectomized animals die apparently from extreme inanition or from intercurrent infection rather than in diabetic coma due to acidosis.

5. When the pancreas remnant is too small to maintain normal sugar tolerance and metabolism, the pancreas rest is more likely to undergo gradual atrophy than to show hypertrophy, with the end result of absolute and fatal diabetes (Sandmeyer). The incomplete diabetes in animals following extirpation of more than 85 per cent. of the pancreas can apparently be intensified, and the appearance of complete diabetes and death hastened by a liberal carbohydrate diet (Thiroloux, Allen).

6. Complete pancreatectomy leads to death in three to eight weeks, in the case of dogs, irrespective of the age of the animal (Carlson), while diabetes mellitus is usually more rapidly fatal in children than in adults and in old people.

7. The persistent hyperglycemia and glycosuria and the low respiratory quotient show that the pancreatectomized animal burns practically no

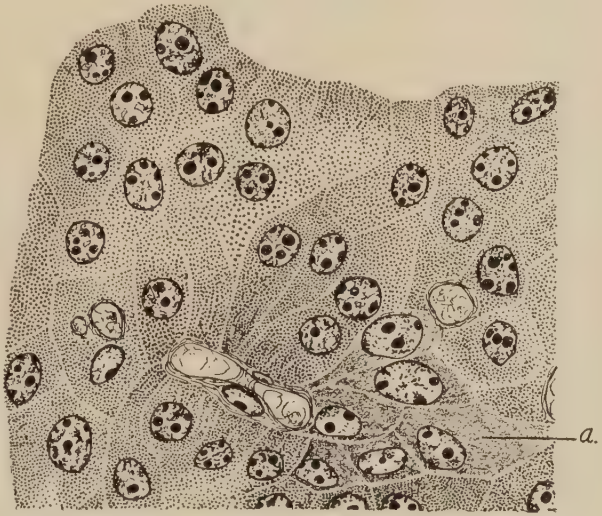


FIG. 17.—SMALL PORTION OF AN ISLET OF LANGERHANS OF THE GUINEA PIG. Shows B cells filled with fine granules, and A cells stained diffusely; a, A cells. $\times 1066$. (Bensley.)

sugar, yet the study of the sugar oxidation capacity of the blood and of individual tissues like the skeletal muscles and the heart have so far revealed no difference between the normal and the diabetic animal (Claus and Embden, Maclean, McGuigan, Patterson and Starling, Macleod and Pearce). The respiratory quotient of the dog's heart averages 0.71, irrespective of whether the heart is that of a diabetic or a normal dog (Starling and Evans).

Certain other features of experimental pancreatic diabetes may be noted. Epstein and Baehr claim that there is an increase in the blood volume (plasma) in dogs and cats after pancreatectomy, irrespective of whether the animal is fed. Hoskins and Gunning state that in dogs after complete pancreatectomy the blood pressure remains either normal or somewhat depressed. Reaction to adrenalin is usually augmented—to

nicotin variable but usually depressed. There is no evidence that the pancreas normally exerts a depressive action on the sympathetic nervous system. They found no evidence of increase in the adrenalin content of the adrenals after pancreatectomy.

Verzar and Fejer claim that administration of glucose during the first three to four days after pancreatectomy raises the respiratory quotient. This, if true, would indicate that the pancreas hormone persists in the blood and the tissues for several days. This is improbable. It must be remembered, however, that all the sugar of the food or from the endogenous protein metabolism does not appear in the urine even in animals and patients showing the D: N ratio of 3:65:1, which Lusk has designated as the index of absolute diabetes. It is not known what becomes of the retained sugar. In diabetic patients "the respiratory quotient fails to account for all the carbohydrates that disappear in the body" (Allen and DuBois).

Numerous attempts have been made to explain the glycosuria of diabetes by the increased rate of liberation of the sugar from some hypothetical sugar-protein or sugar-colloid combinations in the blood. The recent dialysis experiments of Van Hess and McGuigan seem to demonstrate that all the sugar in the blood is present in simple solution, that is, in free form.

The carbohydrate tolerance varies greatly in different species. It is very low in the pig and the sheep (Carlson and Drennan, Hunter and Hill). In normal persons 400-500 grains of glucose may be given by mouth without inducing polyuria or glycosuria (Taylor and Hulton). In normal men and animals the oxidation of sugar is increased in proportion to the quantity of sugar given intravenously up to a very high limit (Woodyatt).

The endeavor to determine how absence of the pancreas causes diabetes is practically a record of repeated failures. The leading idea in all this work has been the internal secretion theory, or that the pancreas yields some substance to the blood in some way necessary for the oxidation of the sugar by the tissue cells. But in the absence of conclusive demonstration of the internal secretion the possibility that the work of the pancreas in maintaining normal sugar metabolism consists of detoxication processes must always be kept in view. The fact that even temporary glycosuria is not induced in normal animals by diabetic blood does not render untenable this hypothesis concerning detoxication processes in maintaining normal sugar metabolism.

The new method of attack introduced by Cohnheim has not yielded consistent results (Claus and Embden, McGuigan) and in the light of the findings of Levene and Meyer the method itself is called in question, as it appears that in a mixture of muscle extract and pancreas extract glucose is polymerized, not oxidized. No light on pancreatic diabetes

has so far been shed by studying the sugar oxidizing power of tissue débris or tissue extracts.

Attempts to Control Experimental Diabetes

Feeding Pancreas or Pancreas Extracts.—Feeding dogs in complete or partial pancreatic diabetes with fresh pancreas increases the glycosuria and acidosis (Sandmeyer, Pflüger, Lüthje, Reach, Rosenberg, Kirk). Cooked pancreas gives equally negative results. Feeding of raw muscle, liver, or other tissue extracts has the same unfavorable influence on the glycosuria and ketonuria. Ausset, and particularly Pratt, Spooner, and Murphy report good effects from feeding pancreas in partially diabetic dogs, but the improvement in the carbohydrate tolerance was slight, variable, and practically negligible.

According to Massagli, feeding pancreas extract to guinea-pigs with experimental reduction of the pancreas reduces or prevents the alimentary glucosuria following carbohydrate food. He advocates the use of pancreas extract in mild cases of human diabetes.

Injection of Pancreas Extracts.—Subcutaneous or intraperitoneal injections of extracts of the pancreas variously prepared may cause a temporary diminution of the glycosuria in diabetic animals (Caparelli, Vanni, Tiberti and Franchetti, Minkowski, Hédon, Scott, Allen, Murlin and Kramer, and others). But this temporary diminution of the output of sugar in the urine is associated with the toxic effects of these extracts, such as depression, fever, etc., and McGuigan has recently shown that anything which causes marked systemic depression (such as injection of proteoses) leads to hypoglycemia, and will thus temporarily diminish an existing glycosuria. Thus Underhill reports diminution of glycosuria in dogs by hydrazin. The after-effects of pancreas extracts given to diabetic animals are a general increase in the glycosuria and ketonuria (Leschke). Knowlton and Starling, and Maclean and Smedley reported that the sugar oxidation of the heart from diabetic animals is almost nil, and in any event much less than that of a heart from a normal animal; but further work has shown these results to be due to faulty technic (Macleod and Pearce, and Patterson and Starling). Extracts of the pancreas added to the perfusion solution has no effect on the respiratory quotient of the diabetic heart (Starling and Evans). *There is no evidence that any extract of the pancreas so far prepared has increased the power of a diabetic animal or patient to oxidize sugar.*

Blood Transfusion.—If the pancreas controls the oxidation of sugar in the tissue by a hormone or hormones, these must be present in the blood, and unless they are extremely unstable or present in very minute traces, it should be possible to increase temporarily the sugar oxidation in diabetic animals and patients by transfusion of normal blood in suffi-

cient quantities. But the results obtained by this method are both conflicting and difficult to interpret.

Lepine reports a temporary diminution in the output of sugar in the urine, but no diminution in the blood sugar. This would seem to point to some injurious action of the foreign blood on the kidneys—a suggestion also advanced by Hédon, but Rabens has shown that transfusion of normal blood into diabetic dogs does not influence the output of any of the urinary constituents except the sugar. Hess injected intravenously 50-150 c.c. of blood from diabetic dogs into normal dogs (on the theory that diabetic blood might stimulate the pancreas to a greater output of internal secretion) and nine to fourteen hours later he injected the serum from this animal into diabetic dogs. The influence on the glycosuria of the diabetic animal was slight or inconstant. In view of the results of Drennan, it seems likely that in the experiments of Hess the pancreas secretion in the blood was destroyed by the delay in centrifuging the blood. Alexander and Ehrmann injected blood from the pancreatic-duodenal vein of normal dogs into diabetic dogs, but obtained no definite or constant decrease of the glycosuria.

Drennan injected 50-150 c.c. of fresh defibrinated dogs' blood into the veins of diabetic dogs and invariably obtained a temporary lowering of the urine sugar and the D:N ratio. Defibrinated sterile blood loses this action on standing for a few hours. The course of the blood sugar in the injected animals was not studied. Hédon has reported a very extensive series of blood transfusions in diabetic dogs. Direct transfusion from a normal dog into a diabetic dog previously bled dry causes a temporary lowering of the blood sugar and decrease or complete suppression of the glycosuria, but since the same results were produced when blood from a diabetic dog was transfused into another diabetic dog Hédon concludes that the temporary diminution of the hyperglycemia and glycosuria following the transfusion were not due to any specific pancreas secretion in the blood but to a lowering of the blood sugar by dilution and to a toxic action of the foreign blood on the kidneys. The results of the cross transfusion experiments reported by Hédon do not concern us here, since these may be interpreted in various ways (detoxication by the pancreas, storage of glycogen in the normal animal, dilution of the diabetic blood, etc.). Hédon also transfused (cross transfusion as well as serum injections) blood from the pancreatic vein of normal to diabetic dogs. A slight temporary lowering of the hyperglycemia with a greater reduction of the urine sugar was noted, but the latter is interpreted as due to an injurious action of the foreign blood on the kidneys. Hédon concludes that the internal secretion of the pancreas acts on and is absorbed by the liver, and is therefore not present in the blood of the systemic circulation. Hédon attempted to obtain evidence in support of this view by introducing a living pancreas in the systemic and in the portal circulation

of diabetic dogs. With the living pancreas interposed in the portal circulation the hyperglycemia and glycosuria were diminished, but interposed in the general circulation the pancreas had no effect.

We do not think that these latter results of Hedon can be accepted, in view of what is known concerning the carbohydrate metabolism in dogs with Eck fistula. In the animal with the Eck fistula the internal secretion of the pancreas, if there is one, must pass into the general circulation, and only a small part of it can reach the liver by way of the hepatic artery, just as in Hedon's diabetic dogs with the living pancreas from another dog interposed in the general circulation; yet the Eck fistula dog does not develop diabetes.

Murlin and Kramer have recently reported one experiment with transfusion of normal blood into a diabetic dog, using the respiratory quotient as a measure of sugar oxidation. The average r.q. for two one-hour periods before the transfusion was 0.678; for four one-hour periods after the transfusion, 0.700. No conclusion can be based on the result of a single experiment, but so far as they go in this case, the transfusion raised the r.q. Murlin and Kramer appear to have had in mind transfusion as "a measure of practical importance" in clinical diabetes, and are therefore disappointed with the results. To our way of thinking this one experiment was sufficiently encouraging to warrant ten or twenty additional ones, in the hope of settling the vexed question of internal pancreatic secretion, whether or not blood transfusion will be a measure of practical importance in clinical diabetes.

Carlson and Ginsburg found that the transfusion without anesthesia or previous hemorrhage of normal blood into dogs in complete pancreatic diabetes causes a temporary (4-8 hours) lowering of the hyperglycemia and the glycosuria. Similar transfusions of diabetic blood into diabetic dogs have no effect on the hyperglycemia.

There was no indication in these results that the sugar retained by the animal in consequence of this temporary lowering of the sugar excretion by the kidneys is subsequently eliminated by the kidneys as excess sugar, as suggested by Murlin.

The blood transfusion as such does not impair the kidneys' activity in any demonstrable way, either in diabetic or in normal dogs. The temporary lowering of the glycosuria of pancreatic diabetes by transfusion of normal blood is due to the diminished hyperglycemia, not to kidney injury, but it remains to be demonstrated that this retained sugar is actually oxidized by the tissues. The sugar might be eliminated into the digestive secretions and destroyed by the bacteria of the digestive tract. In this case it is obvious that the transfusion experiments of Carlson and Ginsburg do not demonstrate the presence of pancreas hormones in the blood. The transfusion does not induce depression, so that the hyperglycemia cannot be ascribed to this general factor.

Parabiosis.—Experimental symbiosis or parabiosis of two mammals is accomplished usually by union of the skin and abdominal walls of two sisters or brothers. It was originally thought that such union of two animals would lead to a direct vascular connection between the two, but it is now known that this is not the case. There is no fusion of the capillary systems of the two animals in the region of the tissue union; but the capillary systems of the two animals are in so close contact that chemi-

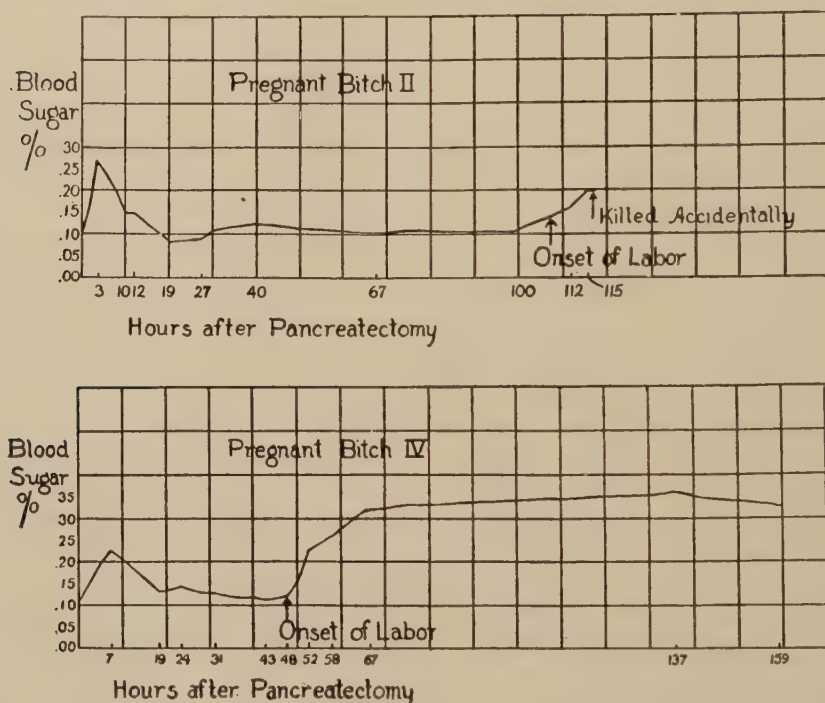


FIG. 18.—CHARTS SHOWING ABSENCE OF HYPERGLYCEMIA AND DIABETES AFTER COMPLETE PANCREATECTOMY IN LATE PREGNANCY. Diabetes begins at onset of labor. (Carlson and Ginsburg.)

cal substances injected into one animal soon appear in the blood of the other animal. On the basis of this fact one may reasonably expect that the blood hormones of one animal would find their way into the body fluids of the other animal.

On this theory Forsbach extirpated the pancreas in one member of two such parabiotic pairs (dogs). In every case a slight temporary glycosuria appeared in both animals. But because of accidents both experiments were terminated before definite results were obtained.

Pregnancy.—It was shown by Pearce that the islets of the pancreas appear early in fetal life. There appears to be no diabetes or glycosuria in human infants born two or even three months before term. This would

seem to show that the pancreas hormones become of functional importance to the fetus a considerable time before the end of gestation. On the basis of these facts Carlson, Drenman, Orr, and Ginsburg made complete pancreatectomy in pregnant bitches near term. *In all cases where this operation is not followed by abortion, the blood sugar and the urine remain normal until the pups are born, or removed by cesarean section.* Complete pancreatectomy in bitches in early pregnancy leads to abortion, or at least to death of the fetuses, in one or two weeks and the course of the diabetes is not influenced.

This absence of diabetes may be due either to the pancreas hormones of the fetuses passing into the mother's blood or to some detoxicating action on the part of the fetal pancreas.

There is a seeming discrepancy between these results on pregnant dogs and the usual clinical experience on the effects of pregnancy on the course of diabetes in the human. The clinical experience appears to be unanimous on the point that pregnancy augments the diabetic symptoms, and hence the practice to terminate the gestation in diabetic mothers. Now, even if in its primary cause all cases of diabetes mellitus are identical with that of experimental pancreatic diabetes, the favorable action of the fetal pancreas on the mother would come only late in pregnancy, and the disturbances in digestion, circulation, and emotional states, etc., of the first half of pregnancy would undoubtedly act unfavorably. But so far as we have been able to learn the unfavorable action of pregnancy on clinical diabetes during the second half of gestation is even greater than during the first half. If this is true, it would seem to indicate a primary difference in the etiology of diabetes in man and of experimental pancreatic diabetes in other mammals. The difference may be only apparent, however. If the diabetes in the mother is caused by the depression of the pancreas by some substance in the blood, or by the inhibition or neutralization of pancreatic secretion by substances in the blood, rather than by actual atrophy of islet tissue, these substances in all probability would act in the same way on the fetal pancreas or pancreatic hormones, thus giving the usual clinical findings.

Transplantation of the Pancreas.—Most of the transplantations of the pancreas have been mere *dislocation* of a portion of it, the usual method being the transplantation of the tail of the pancreas with *its circulation intact*, to other parts of the abdominal cavity, or even under the skin of the abdomen. If a sufficient quantity of the pancreas is thus dislocated or transferred and care is taken to retain the circulation in good condition, at least for a time, the remainder of the pancreas may be extirpated without inducing diabetes (Theroloix, Hédon, Lombroso, Minkowski). But in most cases even these transplants show a tendency to atrophy with a gradual onset of diabetes and ultimate death in complete diabetes. The external ferments of the pancreas are probably responsible

for this gradual necrosis of the graft. There is no record in the literature of transplantation of pure island tissue. There is certainly greater hope of success with such tissue than with the entire pancreas. Pflüger failed to influence the diabetes of depancreatized frogs by inserting pieces of the pancreas under the skin or in the peritoneum. Pratt reports the case of one pancreas autotransplant into the spleen (dog) that retained its function (absence of diabetes) for six months.

THE RELATION OF PANCREATIC DIABETES IN ANIMALS TO CLINICAL DIABETES

In their essential features experimental and clinical diabetes are practically identical. There is the same impairment of power to burn sugar, the identical hyperglycemia, tendency to acidosis, lowered resistance to infection, polyphagia, etc. The two types of diabetes are influenced in the same direction by dietetic and therapeutic measures (Allen). All the evidence points to the view that actual diabetes mellitus in man is primarily due to deficiency or inhibition of pancreatic hormones. This does not apply to the various glycosurias (adrenalin, nervous, alimentary, postoperative, etc.) which do not involve impairment of sugar oxidation.

The main points of difference between experimental pancreatic diabetes in animals like the dog and diabetes mellitus in man are: a lower D:N ratio and a greater increase of total metabolism and less acidosis and an increase of total metabolism in experimental diabetes, together with the fact that human diabetes frequently ends with death before there is any pronounced degeneration in the island tissue, as determined by histological methods. It would seem that, in the absence of intercurrent infections, the human diabetic patient dies from acidosis; the dog with complete loss of the pancreas dies from extreme inanition.

ADMINISTRATION OF PANCREAS PREPARATION IN CLINICAL DIABETES

Administration of Pancreas Preparation by the Mouth.—Some of the earliest attempts to treat diabetes mellitus organotherapeutically were by the administration of the pancreas by the mouth; it was early largely abandoned, for the results were practically negative (Mackenzie, Wood, White, de Cereville, Willis, Williams, Rennie and Fraser, Pratt, Wood, Marshall).

A few writers (Wegele, Meyer, Cowles, Eustis) have reported favorable results. Some of these reports contain only impressions; in others the glycosuria seemed dependent upon an infection and varied so much in severity that it is difficult to determine what, if any, effect the treatment had. In Cowles' case the diabetes had followed an abscess of the pancreas; marked and rapid improvement is stated to have followed the

eating of one to six (average three) raw pancreases of calves daily. After discontinuing the treatment the patient became rapidly worse and died, as he probably would have done even had the pancreas feedings been kept up.

Rennie and Fraser administered the islands of Langerhans obtained from fish of certain species in which they occur separately, i.e., distinct from the pancreas proper, to a number of diabetics; the results were negative.

Sewall found in the earlier stages of one case of youthful diabetes that the urine could be made free of sugar by the administration by mouth of infusions of raw, lean beef followed after some hours by one of pancreas; neither alone was efficacious, and after some months the combined treatment failed. The method was ineffective in a number of other cases. No good results attended the use of the commercial pancreatic powder.

Under the influence of the first report of Knowlton and Starling on the effect of pancreas extract on the sugar consumption of the diabetic heart, Eustis administered 10-20 grains of "an active extract of the pancreas" every four hours on an empty stomach in four cases of diabetes. He reports diminution of the glycosuria in two of the patients, and no effects in the others.

There is, however, according to Falta, a small group of cases of human diabetes in which the administration of pancreas by the mouth gives good results; *this is the result of supplying the external and not the internal secretion of the gland*. Falta refers to those cases in which the pancreas is diseased, so that there is no longer an adequate secretion of pancreatic juice into the intestine; this occurs most frequently when there is complete obstruction of the pancreatic duct. In such cases Falta states that the administration of large doses (ten grams daily) of pancreatin gives excellent results; calcium carbonate is given at the same time.

Subcutaneous and Intravenous Injections of Pancreas Preparations.

—A number of attempts have been made to treat diabetes by subcutaneous and intraperitoneal injections of extracts of pancreas, with negative or injurious results. The favorable results reported by some of the earlier clinicians were shown by Pflüger and by Leschke to be wholly inconclusive. The more recent attempt of Zuelzer to treat the disease by the intravenous injection of a "pancreas hormone" was shown by von Fürth and Schwarz to be based upon a very unsatisfactory theory, and by Forschbach to be positively dangerous.

Gilbert, Carnot, and v. Noorden have attempted to control diabetes mellitus with administration of liver preparations.

Fortunately few attempts have been made to treat human diabetes by transplantation of the pancreas. Fletcher states that Williams, of Bristol, transplanted the pancreatic gland of a sheep under the skin of

the breast and abdomen of a diabetic. The patient died in three days of coma.

Blood Transfusion.—Raulston and Woodyatt appear to be the first to try blood transfusion as a practical therapeutic measure in man. The patient was a man in the thirties, the diabetes of several years' standing with periods of threatening coma. The blood (500 c.c.) was yielded by a two-year-old brother of the patient. The experiment was well controlled. *The blood transfusion augmented all the diabetic symptoms for several days following the operation.*

THE RELATION OF OTHER ENDOCRINE GLANDS AND ORGANS TO EXPERIMENTAL AND CLINICAL DIABETES

In 1908 Eppinger, Falta, and Rudinger advanced the theory that diabetes is not due primarily to the hypofunction of any one endocrine gland (e.g., the pancreas), but to a disturbance of the hormone equilibrium of all the glands—particularly that of the pancreas, thyroid, adrenals, and hypophysis. The specific influence on carbohydrate metabolism of hypo- and hyperfunction of the adrenals, thyroid, and hypophysis has been discussed in the sections on these glands respectively. It now remains to consider whether the hypo- or hyperfunction of any other organ beside the pancreas is capable of so reducing the capacities of the tissues to oxidize sugar that true diabetes follows. A critical analysis of the entire literature, experimental and clinical, seems to warrant the following conclusions:

1. Hypo-activity of the thyroid, the hypophysis, and the gonads may slightly increase carbohydrate tolerance, although further studies should be made on this question by Woodyatt's more accurate method of measuring sugar oxidizing capacity. If true, this may be in reality a thyroid factor, as there is some indication of hypertrophy of the islets, at least after thyroidectomy.

2. Excessive administration of epinephrin, thyroid extract, and possibly hypophyseal extract, may induce temporary hyperglycemia and glycosuria, due to increased sugar mobilization. But there is no evidence that this glycosuria is or passes into true diabetes, that is, lowered power to burn sugar, in the absence of a direct pancreas depression. This applies also to disturbances of the nervous system.

3. The precise influence of the hypo- or hyperactivity of the adrenals, thyroid, and hypophysis on the islets of the pancreas cannot at present be definitely stated, but it is obvious that organs which are as necessary to life, that is, to healthy normal life, as the parathyroids, the adrenals, the hypophysis, and the thyroid will affect the vital processes of the islet tissue, at least indirectly, through the general disturbance of metabolism and the circulation.

After a careful experimental and critical review of the entire question Allen stated recently that the "polyglandular equilibrium doctrine of diabetes has consisted from the first of ingenious but unfounded speculations." We are in entire accord with this conclusion.

The attempt of Pflüger to show that diabetes is due, not to hypofunction or loss of the pancreas, but to interference of nervous reflexes from the pancreas to the duodenum and the liver has already been referred to. Any general reflex theory of diabetes is untenable in view of the fact that *every organ so far investigated continues to oxidize sugar after complete denervation*. The loss of the sugar-oxidizing capacity is therefore a hormone, not a reflex phenomenon.

Other workers have pointed to the probable importance, direct and indirect, of the gastro-intestinal tract in diabetes. Case has recently reported a striking parallel between the severity of clinical diabetes and the degree of ileal stasis. If the ileal stasis is a primary factor this would point to intestinal intoxication depressing the pancreas as a contributory factor in diabetes.

The administration of sodium carbonate reduces temporarily the glycosuria of depancreatized dogs. This fact has led Murlin to suggest that the diabetes following extirpation of the pancreas may be due, in part, to the unneutralized HCl of the stomach secretion. Murlin and Sweet have removed the stomach in depancreatized dogs, and find that the glycosuria is less severe than with the stomach intact. But such animals are probably more depressed than after pancreatectomy alone, and the low output of sugar may be due to this condition.

Summary

1. All the evidence supports the view that some substance or hormone secreted by the islands of Langerhans into the blood is necessary for oxidation of sugar by the tissues. This function is specific for the pancreas. Other endocrine organs may influence sugar metabolism in a superficial way by altering the sugar mobilization (adrenals, thyroid), or by increasing or decreasing the rate of oxidation in the body in general. The rest of the endocrine glands cannot maintain the power of the tissues to oxidize sugar in the absence of the pancreas, and the hypo- or hyper-activity of other endocrine glands does not produce diabetes in the presence of a normal pancreas.

2. While the failure of the tissues to burn sugar in the absence of the pancreas is the central and definitely established fact, there are probably other primary defects and equally important impairments involved in the development of acidosis, increased metabolism, lowered resistance, infection, lipemia, etc.

3. All the evidence points to the view that true diabetes mellitus in

man is primarily the result of pancreatic deficiency (islets), or inhibition of the islet hormones.

4. *There is, at present, no organotherapy of diabetes, experimental or clinical. In view of the successful control of clinical diabetes by diet and starvation, especially as developed by Allen, and in view of the past failures of pancreatic organotherapy both in man and animals, there is no justification even for experimental use of pancreas preparations in clinical diabetes, at least until further light is available from the experimental laboratories.*

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DUODENAL MUCOSA

SECRETIN OF BAYLISS AND STARLING

It is well established that acid chyme in the duodenum is the normal stimulus to the secretion of pancreatic juice and bile. Interaction of the acid with the duodenal mucosa liberates into the blood stream a substance which, circulating through the pancreas, excites the latter to activity. This exciting substance was termed "secretin" by Bayliss and Starling. It can be prepared artificially by macerating duodenojejunal mucosa in 0.4 per cent. hydrochloric acid, neutralizing the boiling mixture, and filtering. A few cubic centimeters of the filtrate injected into a vein produce invariably a powerful secretion of pancreatic juice. That a "chemical messenger," or hormone, is at the basis of the duodenal acid reflex has been proved by even more crucial experiments—transfusion (Wertheimer, Enriquez, and Hallion), cross-circulation (Fleig, Matuso), and perfusion of the isolated pancreas (Huston).

Secretin exists in the duodenal cells in the form of a "prosecretin." Activated by the acid chyme the secretin passes directly into the blood. To the extent that the secretin passes into the lumen of the gut it is a waste, as it is quickly destroyed by trypsin and by pepsin hydrochloric acid digestion, and even in the absence of these digestive ferments secretin is not absorbed in active form from any part of the gut. Giving secretin by mouth is therefore without effect on the activity of the pancreas and the liver. Subcutaneous injections of secretin are also practically without effects.

Secretin is fairly resistant to heat but it is readily oxidized. When injected into the blood the action on the pancreas and the liver is only momentary (a few minutes). That this is not due to fatigue of the pancreas, is shown by the repeated response to repeated injections.

If left standing uncovered for a summer's day, the secretin preparations will become inactive. Even if kept in the ice chest (no other precaution being taken), its activity is lost in a very few days. Sunlight undoubtedly hastens the oxidative process. If care is taken as to sterility and the secretin is kept on ice, well stoppered and in a dark flask,

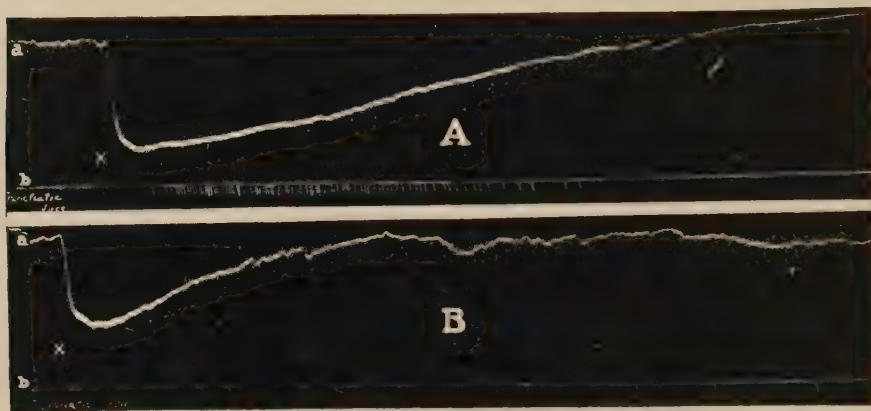


FIG. 19.—TRACINGS SHOWING PRACTICALLY COMPLETE DESTRUCTION OF SECRETIN BY THE GASTRIC JUICE. Dog under light ether anesthesia; cannula in the pancreatic duct; a, carotid blood pressure; b, record of flow of pancreatic juice in drops. Time, twenty-five minutes. Tracing A: intravenous injection of 10 c.c. secretin (prepared fresh from dog's duodenal mucosa) at x. Tracing B: intravenous injection (at x) of 10 c.c. of the same secretin as in Tracing A, after being digested in normal human gastric juice at 37 C. for two hours. (Carlson, Lebensohn and Pearlman.)

it will retain its activity for several weeks. In consequence of the instability of secretin the commercial preparations of secretin so far placed on the market (*secreto*gen, *duodenin*, also the *secretin* of Beveridge) contain, as a rule, no prosecretin or active secretin (Carlson, Lebensohn, and Pearlman).

Secretin has not yet been prepared in pure form. It represents at present a mixture of substances, probably including cholin. Repeated intravenous injections of secretin are therefore highly toxic, producing collapse (Starling).

SECRETIN THERAPY

It is obvious that a rational and useful secretin therapy demands these two fundamental conditions: (I) *deficiency of prosecretin in the duodenal mucosa must be an important factor in the etiology of the disease*; (II) *secretin must be able to influence the pancreas and the liver when given by mouth, for it is not safe to introduce it repeatedly into the*

reins of human beings. Neither of these two conditions has been established. Despite this, secretin, or alleged secretin, has been used in the therapy of a variety of diseases.

Diabetes Mellitus.—Moore, Edie, and Abram were the first to suggest a therapeutic value for secretin, having obtained favorable results with secretin administration in diabetes. They argued that the internal secretion of the pancreas may be stimulated by secretin, and that some cases of diabetes may be due to lack of this necessary excitant. Owing to the importance of the question, their announcement was followed quickly by numerous investigations by other observers.

Previously, Spriggs, at the suggestion of Starling, had tried intravenous injections of secretin, free from depressor substance in a diabetic patient, and had obtained negative results. Moore, Edie, and Abram gave their secretin by mouth over long periods. Of the five cases cited in their first paper, two were negative. The third was that of a man, aged 25, who received daily 30 c.c. of secretin; after a latent period of three weeks, the sugar suddenly fell, and after four months the urine was sugar-free. Six months later a relapse occurred with the development of phthisis and death. The other two patients were a boy, aged 7, and a girl, aged 9, whose urine in from three to five weeks became sugar-free during the secretin treatment, in spite of severe diabetes. One of these patients later relapsed. Bainbridge and Beddard gave secretin a thorough trial in three cases with negative results, and are disposed to attribute the results of Moore to dieting. Dakin and Ransom cited one case, secretin being given for twelve weeks, with negative results; Foster, nine cases, all negative; Charles, three cases, all negative. Crofton, however, gave secretin a trial in one case with favorable results. Moore, Edie, and Abram, in a later paper, report a large number of cases tried with the majority of results negative, though in some cases an improvement in the digestion, and in certain cases an increase of weight was noted.

One method of testing the basis of Moore's theory would be by examining the prosecretin content of the intestine in diabetics. Bainbridge and Beddard found, in the paper referred to, that from five of the six cases of diabetics examined post mortem little or no secretin could be prepared; but in a subsequent report of seven cases they found only one in which the secretin obtained was scanty. The failure to obtain secretin in some cases they claim is probably due to the rapid post mortem degeneration of diabetic tissue. Evans, in Starling's laboratory, stated that in dogs made recently diabetic by total pancreatectomy, but little secretin could be obtained; Hédon and Lisbonne, and Pemberton and Sweet report, on the contrary, that the duodenum of diabetic dogs is rich in prosecretin. Bainbridge and Beddard, working on a diabetic cat, likewise found prosecretin to be present in normal quantity.

Digestive Disturbances.—Secretin for digestive disturbance was first

used in the "acid duodenal medication" of Enriquez. This consisted in the giving of tartaric acid in thick keratin capsules, the acid not being liberated until the duodenum was reached, where it provoked the formation of secretin. "The secretin mechanism," he says, "is probably capable of pathologic disturbance as would result, for example, with diminished acidity of chyme, disturbance of the normal motility of the stomach or pylorus, or diminished prosecretin in the mucosa. Such a condition would produce disturbance of the pancreatic, biliary, and intestinal secretions, and interfere with intestinal movements, with a clinical syndrome of intestinal dyspepsia as a result, among the chief and most constant symptoms of which would be constipation." "The acid duodenal medication" was submitted to wide clinical use, and very favorable results in certain obstinate cases of constipation were reported. In regard to "diminished prosecretin in the mucosa," Wentworth has claimed that in infantile atrophy such is the condition, but Sweet and Pemberton have found that the difficulty of preparing secretin from human duodenums is such as to render Wentworth's findings inconclusive.

Beveridge suggests the use of secretin in pyloric stenosis, pancreatic insufficiency, cirrhosis of the liver, colonic stasis, in gastro-enterostomy and short-circuiting of the intestines. Harrower has advocated the use of secretin for a large number of maladies.

Summary

1. There is no rational or useful secretin therapy at present. There is no reliable evidence that secretin or prosecretin deficiency is a factor in disease. Secretin has not yet been placed on the market in stable form. It is, at present, not safe to administer secretin intravenously; and given by mouth secretin is rapidly destroyed by the digestive enzymes, and in any event not absorbed in active form into the blood. Hence secretin given by mouth is without effect on the pancreas and the liver.

2. *The Alleged Gastro-intestinal Motor Hormone of the Mucosa.*—Heidenhain showed more than twenty-five years ago that intravenous injections of tissue extracts cause a temporary intestinal peristalsis, defecation, vomiting, etc., probably due to asphyxia from the greatly lowered blood pressure, besides a number of other untoward symptoms. In 1904 Henriques and Hallion showed that by treatment of strips of gut with Ringer's solution or distilled water a substance may be extracted which stimulates contractions in another intestinal strip.

Similar results were observed when the extract was injected into normal intact animals. This stimulating action is prevented by atropin. In 1908 Zuelzer proposed, on the basis of badly controlled animal experiments, the novel theory that there is a specific gastro-intestinal motor hormone elaborated in the intestinal mucosa during digestion, absorbed

into the blood, and stored in the spleen. Hence the spleen was held to contain more of this alleged hormone than any of the other organs. It was claimed that an extract of spleen and intestinal mucosa ("hormonal") on intravenous or intramuscular injection produces normal intestinal peristalsis in man and animals, without any injurious side effects. The extract was tried for a time, especially in Germany, in cases of chronic constipation, and postoperative intestinal stasis. It was soon found that intravenous injections of this extract in patients may cause shock, collapse, and sudden death. And the more carefully controlled investigations of Dittler and Mohr, Sabatowski, Schlagenweit, and others showed that intramuscular injections of the extract have little or no action on gastro-intestinal motility, while the intravenous injections produce the general toxic symptoms characteristic of all tissue extracts. Hence there is no specific or physiological motor hormone in the duodenal and spleen extracts.

After careful perusal of the entire "hormonal" literature we are impressed with the uniformly favorable results first reported by Zuelzer and a host of other clinicians in two important classes of cases, viz., chronic constipation and postoperative intestinal stasis. These results were undoubtedly due to suggestion and dictated by uncritical enthusiasm, faith, and hope in a new remedy. When critical judgment returned, "hormonal" was speedily found not only wanting but dangerous. The "hormonal" therapy had no basis in physiology or pathology. It was not based on well controlled experiments on animals. So after a brief popularity with the credulous clinician, it passed naturally to the therapeutic bone yard. "Hormonal" cannot do anything with gastro-intestinal motility that cannot be accomplished, and with greater safety, by such drugs as pituitrin, pilocarpin, or eserine.

3. *Other Possible Hormone Functions of the Intestinal Mucosa.*—The work of Draper, Matthews, and especially that of Whipple and his collaborators on duodenal extirpation and duodenal obstruction has suggested hormone functions of the duodenal mucosa other than those concerned with secretin and enterokinase. Matthews claims that extirpation of the upper part of the duodenum in the dog invariably leads to death within three days; hence he concludes that the duodenum is as necessary for life as the adrenals or the parathyroids, presumably through hormone function. But others claim that animals live indefinitely after duodenal extirpation (*cf.* Minkowski). Draper reports that feeding duodenal mucosa to dogs with duodenal obstruction or a closed duodenal loop lengthens the life of the animal somewhat, but fails to prevent death. These experiments by Draper are not convincing. Whipple reports the secretion or production of a toxic substance (protein split product) in closed intestinal loops, and successful immunization of dogs against this toxin. It is held by others that the toxins in closed intestinal loops are developed

by bacteria acting on the impaired mucosa, or by autolysis of the impaired mucosa (Dragstedt). The entire problem is still under investigation, and *the experimental work so far has yielded nothing in the way of hints of useful organotherapy of intestinal stasis, and intestinal obstruction.*

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THE SUPRARENAL GLANDS

Physiology.—The suprarenal glands of man and the higher animals consist of two distinct tissues. The cortex is of mesodermal origin and belongs to a system known as the *interrenal system*. The medulla is of ectodermal origin, originating as a part of the sympathetic nervous tissues. It is a part of the “adrenal” or “chromaffin” system (so called from its affinity for the salts of chromic acid). A very considerable amount of chromaffin tissue is found in man outside of the suprarenals (in small masses along the sympathetic nerves and in the carotid gland); interrenal tissue is also often found in other parts of the body outside of the suprarenals.

These two parts are anatomically separated in some fishes, but in man and the higher animals they are so intimately connected

that it is very difficult to study their functions separately, and most of the knowledge on this subject is based upon observations and experiments upon the entire organ. Accessory suprarenals (medullary tissue, or cortical tissue, or both combined) occur in some animals, particularly the rat.

The cortex is made up of polygonal epitheliumlike cells arranged in columns, and rich in a double refractive lipid substance. In the pig this lipid makes up 38.8 per cent. of the dry cortical residue (Biedl). In

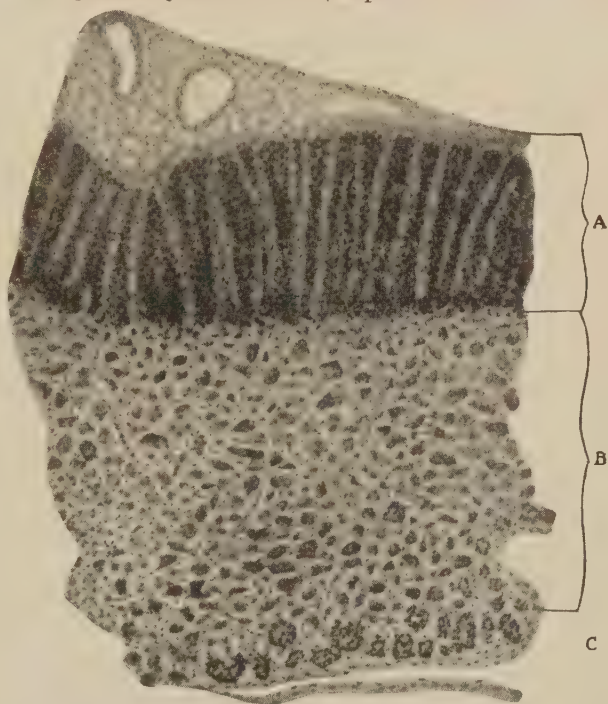


FIG. 20.—SECTION OF SUPRARENAL OF CHILD TWELVE DAYS OLD, LOW POWER. (Elliott and Armour.)

A, outer part of cortex; B, large cells forming boundary zone of cortex; C, thin layer of medulla: just below is the central vein.

man there occur certain degenerative changes that lead to diminution of the adrenal cortex during the first two weeks after birth (Lewis and Pappenheimer). The modified nerve cells of the medullary portion are characterized by their brown color reaction with chromic acid (chromaphile reaction). This chromaphile tissue has been found in certain parts of the nervous system and in the skin of various invertebrates. In the American toad (*Bufo aqua*) it is present in part of the skin, and the skin secretion of this animal contains epinephrin (Abel).

The suprarenal gland has a very rich blood and nerve supply. According to Neumann the blood supply to these glands is greater than to any other organ in the body, or 6-7 c.c. per gram of gland per minute. This enormous blood supply is undoubtedly of significance in relation to the secretory and, possibly, detoxicating functions of the gland.

Each adrenal gland receives numerous nerve filaments from the splanchnic nerves and the adrenal plexus. The nerve filaments are distributed both to the cortex and the medulla, part of the fibers passes to the blood vessels (vasomotor nerves) and part appears to end around the gland cells (secretory nerves?). True sympathetic nerve cells are also found both in the cortex and the medulla.

The Chemistry of the Medullary Tissue.—Oliver and Schäfer made the very important discovery that extracts of the medulla of the suprarenal glands, when injected intravenously, cause a marked rise of blood pressure.

The chemical work of Abel, von Fürth, Takamine, Aldrich, Dakin, Stolz, Flücher, and others resulted in the isolation of and, later, synthesis (from coal tar derivatives) of a definite chemical compound named by Abel *epinephrin*, by Takamine *adrenalin*. Chemically this compound is dioxyphenylethylolmethylamin ($C_9H_{13}NO_3$). It is levorotatory. The compound made synthetically is optically inactive, and has only about one-half of the physiological activity of the natural compound (Cushny, Schultz); it can, however, be separated into two optically active isomers, one of which, the levo-compound, is identical in every respect with the natural base. Epinephrin is present in all chromaphile tissues (Vincent, Fulk and Macleod). It appears very early in the fetal adrenals, at least in most species (McCord, Fenger, Cevolatto, Langlois and Rehns). But in a very careful and critical work Lewis failed to detect epinephrin in the fetal adrenals in man. This is important in view of the fact that there is no evidence of adrenal insufficiency in prematurely born infants. If epinephrin is absent in the human fetus in late gestation (7-8 months), this substance is evidently not necessary for life.

It is estimated that the normal adrenals of adult persons contain at any one time only a few milligrams (4-5) of epinephrin (Elliott). The adrenals of normal dogs contain 1-2 mgs. epinephrin (Sydenstricker.) Trendelenburg found that the adrenals of the cat secrete into the blood about 0.003 mg. epinephrin per minute or about 5 mg. per kilo body weight

in twenty-four hours. Hoskins and McClure estimated the output of epinephrin in the dog as 0.2 c.c. of a 1:1,000,000 dilution of epinephrin per minute per kilo body weight. The same authors found that the blood of the general circulation (dog) contains epinephrin in the concentration of 1:200,000,000. Trendelenburg states that the epinephrin content of the carotid blood of the normal rabbit does not exceed one part to two milliards of blood.

Epinephrin is a rather unstable body. It is oxidized or destroyed only slowly in the blood, but rapidly by the tissue and the walls of the blood vessels (Tatum). Hence giving epinephrin by mouth is practically without physiological effects.

The Secretion of Epinephrin.—It is well established that the suprarenal glands under normal conditions secrete epinephrin into the blood of the adrenal veins continuously. It was formerly supposed that enough epinephrin is thus secreted by the normal adrenals to maintain a steady stimulation of or tonic action on the heart and the blood vessels, thus aiding in the maintenance of the normal blood pressure. This constituted the so-called *tonus theory of adrenal function*. The recent work of Cannon, Hoskins, and others has rendered this tonus theory untenable, for the following reasons:

1. The quantity of epinephrin secreted into the blood under ordinary conditions is too small to affect the heart or the blood vessels. Hoskins found that it requires 0.42 c.c. of a 1:1,000,000 epinephrin per kilo body weight per minute to affect the blood pressure in the dog, and *this minimum quantity causes vasodilatation, not vasoconstriction* (Cannon, Hoskins). The normal output of epinephrin by the dog's adrenals is only 0.2 c.c. of this epinephrin concentration per minute.

2. The quantity of epinephrin in the blood sufficient to raise the blood pressure or to affect the blood pressure is more than sufficient to inhibit the motility of the gastro-intestinal tract. In fact the gastro-intestinal tract is more sensitive to the inhibitory action of epinephrin than the heart and the blood vessels to its tonic or stimulating action. *Hence as long as gastro-intestinal motility is present there is not enough epinephrin in the blood to influence the tone of the heart and the blood vessels.*

Stimulation of the splanchnic nerves (direct, reflex, or through cerebral processes of strong emotional tone, such as fear, pain, anger, etc.) increases the output of epinephrin by the gland (Biedl, Dreyer, Cannon, Elliott, and others). It is generally assumed that this is a true secretory action of the adrenal nerves on the medullary cells. But the stimulation of the splanchnics causes at the same time vasodilatation in the suprarenals, while it is well known that this stimulation induces vasoconstriction in all the other abdominal organs innervated by the splanchnic nerves. It is not known whether the increased blood flow through the glands by hormone action increases the epinephrin output.

This generally accepted view that painful sensory stimuli, intense emotions, and asphyxia increase the output of epinephrin has recently been questioned by Stewart and Rogoff on the basis of a series of careful experiments. It would seem that the work of Elliott, Cannon and others was not adequately controlled.

Richards and Wood report that stimulation of the depressor nerves leads to a decreased output of epinephrin; they interpret this as a true reflex inhibition of the action of the secretory nerves. However, it is clear that the changes in the blood flow through the gland may be responsible for the change in the secretion rate. Pende claims that section of the splanchnic nerves leads eventually to atrophy of the medulla. This is probably erroneous.

Various other conditions affect the rate of epinephrin output into the blood and the quantity of epinephrin in the gland. Surgical and traumatic "shock" reduces the epinephrin content of the glands to only a fraction (8 per cent.) of their normal amounts (Corbett). Shock induced by hemorrhage or manipulation of the viscera increases the epinephrin content of the blood coming from the glands up to thirty times the normal (Bedford and Jackson). Stewart, Rogoff and Gibson found that massage of the suprarenals increases the secretion of epinephrin.

All anesthetics decrease the epinephrin content of the glands (Graham) presumably through a preliminary increased secretion. But depression of the rate of building up the secretion in the gland may also be a factor. The epinephrin content of the glands is also greatly decreased in all infectious diseases—especially the acute infections such as peritonitis (Elliott, Reich and Berenegowski, Kindley, and others). This is a fact of great practical importance, because of the possibility that suprarenal deficiency may thus be a factor in the debility and prostration of acute infections.

Pellegrini states that the amount of chromaffin tissue is reduced by starvation.

According to Ott and Scott, and Gley and Quinquad, extracts of pancreas, liver, thyroid, thymus, gonads, kidneys, pituitary, parathyroid, etc., cause an increased output of epinephrin. Evidently this is a toxic action of protein-split products in the tissue extracts acting via the vasomotor center and the splanchnic nerves, and possibly directly on the medullary cells. It is of no significance in the relation of these organs to the normal work of the suprarenals.

Dale and Elliott have suggested that some of the general systemic actions of alkaloids like nicotin and pilocarpin, and the anesthetics (morphia, chloroform, and ether) are indirect effects due to the increased output of epinephrin caused by these substances.

There appear to be no seasonal variations in the epinephrin content of the adrenal gland (Seidell and Fenger).

The Physiological Actions of Epinephrin.—Knowledge of the details of the physiological action of epinephrin has increased greatly within the last few years, and it is now possible to bring nearly all the facts accumulated (more especially by Schäfer, Langley, Elliott, Brodie and Dixon, Dale, Cannon, and Hoskins) together and express them in the form of a general law: *the peripheral effects of epinephrin are everywhere essentially the same as those of the stimulation of the sympathetic nerves to the tissues involved.* The action is peripheral, and upon what is known as the “myoneural junction,” which is a part of the “receptive substance” (Langley) of the cell.

The following illustrations show some of the applications of this law:

BLOOD VESSELS.—It has been known for some time that the very great rise of blood pressure following the intravenous injection of epineph-

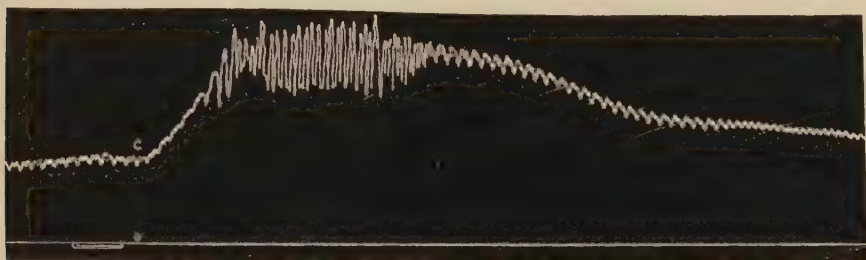


FIG. 21.—EFFECTS OF INTRAVENOUS INJECTION OF ADRENAL EXTRACT (EPINEPHRIN) ON THE HEART AND THE BLOOD PRESSURE. (Oliver and Schäfer.)

rin is due largely to a peripheral constriction of the blood vessels, especially of those of the splanchnic area. The vasoconstrictor muscles of the blood vessels are innervated by the sympathetic nervous system. In organs (heart, lungs, brain) in which the sympathetic vasoconstrictor innervation is but slightly developed (or, according to some writers, absent) epinephrin has but little (according to some, no) vasoconstricting effect (*cf.* Wiggers).

Meltzer and others pointed out that epinephrin may cause a vasodilatation in certain cases, and recently Dale has brought forward further evidence that there is a sympathetic vasodilator (inhibitory) innervation of certain vessels; these dilate under the influence of epinephrin and of the stimulation of the sympathetic nerves if the effects of the constrictor fibers are excluded by the action of ergotoxin. The minimum effective dose of epinephrin always causes a primary vasodilatation (Cannon, Hoskins). All strengths of epinephrin cause dilatation of the blood vessels in the skeletal muscles.

In this connection it may be remarked that the effect of epinephrin upon the blood pressure of animals constitutes a useful method for determining the relative strength of different preparations of this drug; its

effect upon isolated arteries is a very delicate method of detecting its presence (Meyer's method).

The vasoconstricting action of the drug is seen when it is applied to a mucous membrane or to the abraded and bleeding skin; the structures become blanched and hemorrhages from small vessels cease.

HEART.—Extracts of suprarenal and epinephrin cause a marked acceleration and strengthening of the heart beat; the effects are the same as those of the stimulation of the accelerators (sympathetic motor nerves). The maximum rate reached is the same as the maximum rate after stimulation of the accelerators; this rate may be maintained for some time by the repeated injections of small doses (Hunt).

In the intact animal the acceleration of the heart is frequently (almost always, if the dose is large) prevented, at least at first, by a simultaneous stimulation of the vagus centers; the latter is attributed in part to the high blood pressure, but there is some direct action of epinephrin both on the vagi centers and on the respiratory centers (Brown, Nice and Rock).

ALIMENTARY TRACT.—The effect of epinephrin on the alimentary tract is throughout the same as that of the sympathetic nerves. When the latter cause inhibition, epinephrin does also; when the stimulation of the sympathetic causes contraction, epinephrin does the same. Thus in the rabbit, epinephrin causes relaxation of the entire alimentary tract, with the exception of the pyloric, ileocecal, and internal anal sphincters, which contract under its influence. The action of the sympathetic nerves on the alimentary tract varies in different species of animals; the effects of epinephrin vary in a corresponding manner.

Cannon and de la Paz believe that the inhibition of the intestinal movements which results from strong emotions is due, at least in part, to increased secretion of epinephrin; they have shown the latter to occur during fright. These authors suggest the use of strips of the intestine as a very delicate test for the presence of epinephrin, especially in blood.

THE CORONARY CIRCULATION.—Epinephrin contracts the coronary vessels in man and the monkey, but in other mammals (dog, cat, rabbit, ox, sheep, pig) it dilates the coronary vessels (Barbour and Prince). These differences are probably due to the character of the sympathetic innervation of the coronary vessels.

URINARY BLADDER.—The same relations hold for the bladder as for the alimentary tract; in those animals in which stimulation of the sympathetic causes relaxation of the bladder and contractions of the urethra, epinephrin does the same; when stimulation of the sympathetic is without effect upon the bladder, epinephrin is also without effect.

UTERUS.—The effect of epinephrin upon the uterus is determined by the character of the sympathetic innervation. It, like the stimulation of the sympathetic, causes powerful contractions of the pregnant uterus and of the non-pregnant uterus in certain animals. In the virginal uterus of

the cat, however, both epinephrin and stimulation of the sympathetic cause relaxation. Dale was able to demonstrate the presence of a sympathetic inhibitory supply to the uterus of other animals also. After very large doses of ergot, which paralyze the motor nerves, stimulation of the sympathetic or the administration of epinephrin causes relaxation of the uterus in all cases. The conditions are analogous to those which hold for certain blood vessels.

The action of epinephrin upon the uterus is one of the most delicate

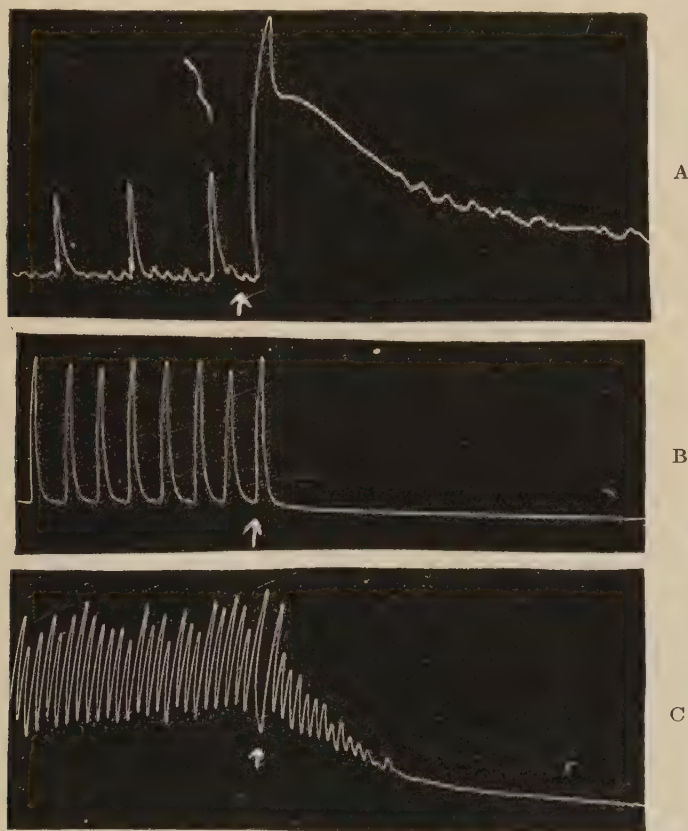


FIG. 22.—A, STIMULATION EFFECT OF EPINEPHRIN ON THE RABBIT'S UTERUS. (Itagaki.) B, INHIBITORY EFFECT OF EPINEPHRIN ON THE UTERUS OF THE RAT. (Itagaki.) C, INHIBITORY EFFECT OF EPINEPHRIN ON THE CAT'S INTESTINE. (Young.)

tests for the drug (Fränkel's test); a solution containing one part in twenty millions is active.

BRONCHIAL MUSCLES.—The effect of epinephrin upon the bronchial muscles is of special interest, since it appears that attacks of bronchial asthma in man are temporarily relieved by it. This suggests the presence of sympathetic inhibitory nerves to the bronchial muscles, but attempts to demonstrate their existence have been unsuccessful. Similarly, efforts to

demonstrate an action of epinephrin upon the bronchial muscles have usually failed. Eppinger and Hess, however, believe that epinephrin may, through the stimulation of sympathetic inhibitory nerves, counteract the contractions of the bronchial muscles caused by increased vagus tonus. Januschke and Pollak found it to relax the bronchial muscles in muscarin asthma and to have some relaxing effect in normal animals.

ACTION ON THE EYE.—The intravenous injection of epinephrin into animals causes the same changes in the eye as follow the stimulation of the cervical sympathetic nerve, viz., retraction of the nictitating membrane and of the eyelids, protrusion of the eyeball, and dilatation of the pupil (through stimulation of the dilator muscle). Instillation of epinephrin into the eye is far more effective in causing dilatation of the pupil when the superior cervical ganglion has been extirpated than it is in normal animals (Meltzer and Auer); this reaction has been utilized in locating the site of injuries to the cervical sympathetic (Cords, Sebileau and Lamaitre). Solutions of epinephrin applied repeatedly to the normal human eye cause dilatation of the pupil (Schultz, Wessley). Slight lesions of the cornea greatly facilitate the reactions; Cords has used the reaction to detect erosions and ulcers of the cornea.

The pupil is said to be abnormally sensitive to epinephrin in some cases of diabetes mellitus and of Graves' disease (Loewi's reaction), and in dementia precox. Loewi considered this increased sensitiveness of the pupil to epinephrin in Graves' disease to be due to an increased irritability of the sympathetic nerves caused by the condition of the hyperthyroidism.

The pupil of the frog's eye (either *in situ* or enucleated) dilates upon the application of very minute amounts of epinephrin; Meltzer and Auer suggested that this reaction might be used for the detection and estimation of this substance. The reaction was elaborated by Ehrmann, and has been frequently used in the study of various problems connected with the suprarenal glands; it has, however, a number of limitations which have not always received sufficient consideration at the hands of some investigators. Injection of epinephrin causes a temporary secretion of the lacrimal and salivary glands and of bile.

THE KIDNEYS.—According to Cow, epinephrin passes directly into the blood of the renal arteries and by its local vasoconstrictor action diminishes the rate of urine secretion, thus acting as an *important control of kidney activity*. But it is difficult to see how this is possible on the basis of the relation of the adrenal veins to the kidney arteries. And in the general arterial blood there is not enough of epinephrin present to act on the renal arteries.

METABOLISM.—Epinephrin has little effect upon nitrogen metabolism except in inanition, when it causes a considerable increase in protein metabolism; this effect is attributed by Eppinger, Falta, and Rudinger to a stimulating action upon the thyroid. Cannon has recently reported

that intravenous injections of epinephrin induce temporary electrical changes in the thyroid gland, which he interprets as due to increased thyroid activity. But there is no antagonistic action of the thyroid or the parathyroid glands to epinephrin glycosuria, as determined by the reaction of the animal after extirpation of these glands (Blum and Mark). Wolf and Thatcher found the nitrogen metabolism normal in a case of Addison's disease. The endogenous metabolism, as represented by creatinin and uric acid, was below normal.

Epinephrin has a marked effect upon the glycogen-sugar mobilization in the body. This is thought to result from the stimulation of certain sympathetic nerves. The epinephrin glycosuria is accompanied and caused by a hyperglycemia and a diminution of or disappearance of glycogen from liver and muscle. The degree of glycosuria is largely determined by the amount of glycogen in the liver, although some excretion of sugar is caused in starving animals.

Zuelzer, Embden, and others have found that when epinephrin is added to blood used in perfusing an excised liver, it causes the latter to liberate sugar into the hepatic vein in far greater amounts than when normal blood is used.

The above facts lead to the conclusion that the action of epinephrin in producing glycosuria is due to a setting free or mobilization of the sugar stored as glycogen. Several recent writers (Underhill and Closson, Macleod, Frank and Isaac) have attributed epinephrin glycosuria to the effect of stimulation of sympathetic nerves going to the liver; this would bring this action in line with the other effects of epinephrin.

Epinephrin glycosuria is said to be more pronounced in animals deprived of their pancreas; it is not easily produced in Addison's disease, unless glucose is given at the same time (Pollak).

It must be noted, however, that the above effects of large doses of epinephrin intravenously on glycogenolysis are, strictly speaking, artefacts. There is no evidence that such amounts of epinephrin are under any conditions put into the blood by the glands in the intact animal. The specific antagonistic action of the suprarenal and the pancreatic secretions on sugar metabolism advanced by Falta and others has proved to be erroneous (Mann and Drips). Epinephrin administration does not effect the oxidation of the sugar in the body (Lusk). Epinephrin deficiency causes no permanent change in carbohydrate tolerance (Crowe and Wislocki). The failure of pancreas extirpation to cause diabetes after previous adrenalectomy in some species is due to the low blood pressure and the moribund condition of the animal (McGuigan).

Epinephrin in certain concentrations (intravenously) increases the coagulability of the blood (Cannon and Mendenhall). In larger doses the coagulation is delayed. According to Cannon, adrenalin also acts as a stimulant to the skeletal neuromuscular mechanism, and he interprets this

as due to a direct action of epinephrin on the muscle; but this has recently been questioned by Schäfer. The improved circulation and the mobilization of the blood sugar may be the factor in delaying fatigue after large epinephrin injections. Epinephrin induces vasodilatation in the skeletal muscles (Hoskins, Gunning, Berry).

The Emergency Function Theory of Epinephrin Secretion.—We have seen that in the normal animal under ordinary conditions there is a continuous secretion of epinephrin, but not in sufficient quantities to have demonstrable physiological effects. Under all conditions that involve great emotional and circulatory disturbances, such as pain, fear, anger, intense physical and mental efforts, etc., there may be a sufficient increase of epinephrin output to temporarily stimulate circulation, increase the blood sugar, and increase the coagulability of the blood. Such temporary changes are obviously of advantage to the animal for successful flight or fight, as Cannon has pointed out, and thus developed his *emergency theory of suprarenal function*. It must be noted, however, that this emergency theory does not touch the essential and constant rôle of the adrenals in the organism, the loss of which invariably leads to death in a few hours or a few days, even if the animal is protected from fight and flight.

The Theory of Epinephrin Control of the Functions of the Blood Capillaries.—Extensive studies on dogs, cats, and rabbits led Gradinescu to conclude that the suprarenal secretion controls metabolism by controlling the permeability of the blood capillaries, and hence the exchange between the blood and the tissues. He claims that adrenal deficiency causes the blood plasma to pass into the tissue spaces and the body cavities to such an extent that the concentration of blood corpuscles becomes twice as great as the normal. The viscosity of such blood is obviously great and the circulation correspondingly impeded. But it is possible that the transudation of plasma from the blood noted by Gradinescu is in reality an effect from the impaired circulation (cardiac edema). But Donath maintains that change in capillary permeability is a factor.

The Functions of the Adrenal Cortex.—Concerning the rôle of the adrenal cortex we have a number of theories, but very few facts. No internal secretion has so far been demonstrated. Whipple has obtained an extract from the cortex having a pituitrinlike action on the circulation. The abundance of lipoids in the cortical cells has led to the suggestion that the cortex elaborates these for the use of distant organs. It has also been supposed, without evidence, that the procurors of epinephrin are elaborated in the cortex. In the absence of definite internal secretions of the cortex theories of detoxicating functions have been advanced (Loewi and Geltwert).

All the evidence, experimental and clinical, to date, points to the cortex rather than the medulla as the organ essential to life (Biedl, Scott, and others). In nearly complete adrenalectomy only the cortical remnants undergo hypertrophy (Crowe and Wislocki).

The most striking correlation of the adrenal cortex appears to be with the gonads. Estrus (male and female), pregnancy, lactation, and gonadectomy are accompanied by increase in cortical substance. Tumors and hyperplasias (hypernephroma) of the cortex may be accompanied by precocious sex development (secondary sex characters) both in the male and the female (Jump, Beates, and Babcock, Baldwin, and others). But these relations are not of a direct and compensatory character. For the adrenals fail to maintain sex life after gonadectomy, and the gonads fail to maintain life itself after adrenalectomy.

Most of the conditions that lead to diminution of medullary epinephrin (such as acute infections) cause at the same time changes in the adrenal cortex, loss of cortical lipoids, etc. (Weltman, Hirsch, and others).

Extirpation of the Suprarenals.—The removal or destruction of both suprarenals leads to death within a few hours or days (Brown-Séquard); exceptions to this rule are due to the presence of accessory glands. Biedl describes the effects as follows: for one to two days the animals seem to be entirely normal; on the second or third day there is loss of appetite; afterward apathy and muscular weakness become apparent; the movements become stiff and uncertain. Then great prostration follows, the animal is unable to rise, and lies extended on its abdomen. There is a marked fall of temperature (to 30° C. or under), respiration is labored, the heart is irregular and weak; the animal usually dies (in one to three days) in this condition of paralysis. Occasionally there are muscular twitchings, more rarely convulsions. Gradinescu states that after complete adrenalectomy rabbits die within seven hours, dogs in ten, and cats within forty-five hours. Removal of one adrenal has no effect. On removal of the second adrenal the animal usually lives longer than when both glands are extirpated in one operation. Elliott reports that complete extirpation of the adrenals in the cat leads to death with low blood pressure, fall of temperature and great depression of vasomotor and cardiac accelerator nerves. But Hoskins and Wheelon state the vasomotor system and the vascular musculature are unimpaired at a time when marked asthenia of cardiac and skeletal muscles is in evidence. Hence there is no evidence that the sympathetic system suffers *primarily* in any degree from adrenal extirpation.

Injections of epinephrin do not increase vasomotor irritability (Hoskins and Rowley). Complete ligation of the adrenal blood vessels leads in a few hours to a distinct fall of blood pressure, but there is no evidence that this fall is due to lack of epinephrin (McGuigan and Mostrom).

Bierry and Malloisel and Porges have reported a condition of hypoglycemia after adrenalectomy. But this is probably not specific, for any condition that induces a marked general depression is accompanied by hypoglycemia (McGuigan). Porges found hypoglycemia in three cases of Addison's disease. The reduced amount of sugar in the blood has been held to explain, in part, the most striking symptoms

following the removal of the suprarenals—the asthenia. Favorable results in Addison's disease are reported from the administration of sugar (Pitres and Gautrelet). Animals deprived of their suprarenals are easily fatigued; if forced to exercise they may die suddenly.

Crowe and Wislocki report enlargement of the lymph glands in adrenal insufficiency. Loewi and Geltwert state that the blood of cold blooded animals from which the adrenals have been removed is toxic. When applied to the heart, the heart stops in diastole, evidently by vagus stimulation, as this toxic action is abolished by atropin. Whipple and Christman state that adrenal deficiency leads to impairment of the liver, as determined by the phenolphthalein test. This is probably an indirect effect of impairment of the circulation.

The questions as to which part of the suprarenal system, the interrenal (cortical) or the adrenal (medullary), or whether both are essential to life, has been much debated; some authors have considered that only the

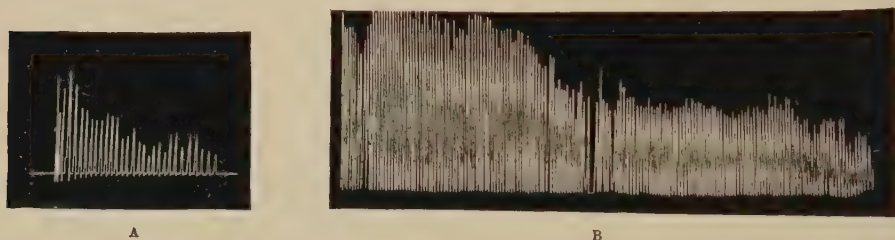


FIG. 23.—A, ERGOGRAF TRACING FROM A PERSON SUFFERING FROM ADDISON'S DISEASE. B, TRACING FROM THE SAME PERSON AFTER SIX WEEKS' ADMINISTRATION OF SUPRARENAL. (Langlois.)

former, others that only the latter, is essential to life. All the evidence points to the cortex as the essential part, but if there is any truth in Gradinescu's theory of epinephrin control of capillary permeability, it is evident that the medulla is also important if not necessary to life.

Disease of the Suprarenal Glands.—The first important contribution to the knowledge of the function of the suprarenals was the classical paper of Addison (1855) on the disease which bears his name. The disease is characterized by a condition of muscular and cardiac weakness, usually with a low blood pressure, a subnormal temperature, apathy, disturbances of the digestive tract (vomiting and diarrhea), pigmentation of the skin and mucous membranes, and a progressive cachexia almost always ending in death. But there may be periods of spontaneous but temporary improvement. Ticken reports a case of apparently permanent (2 years) recovery from Addison's disease. All the features of adrenal disease in man are reproduced by adrenal extirpation in animals, except the skin pigmentation. This may be due to the speedy fatality of complete adrenalectomy; it evidently requires more time for effecting the change in skin pigmentation.

The typical anatomical change found in the suprarenals in Addison's disease is a tuberculous degeneration. The chromaffin tissue in connection with the sympathetic nerve, outside of the suprarenal glands, has also been found involved in a number of cases; in others the chromaffin tissue both in and outside of the suprarenal glands was apparently intact. It is not possible at present to determine whether Addison's disease is due primarily to an involvement of the chromaffin (adrenal) tissue or to that of the interrenal system, or to both.

Absence of epinephrin has been found in a number of cases of Addison's disease (Oliver and Schäfer, Luksch, Ingier and Schmorl).

Studies of other abnormal conditions of the suprarenal glands in man have only been suggestive of possible functions of these organs. It has long been known that in many cases of congenital malformations (anencephaly, hydrocephalus) the suprarenals show a condition of hypoplasia or of aplasia; in some of these cases only the medulla was involved, the cortex being normal. The relations of these conditions, whether causal or not, have not been definitely determined. On the other hand, excessive growth has been reported in cases of tumors of the suprarenals.

Hypoplasia of the suprarenals has been met in a few cases of retarded sexual development, and in cases of osteomalacia and status lymphaticus. On the other hand, hypernephromas originating from cortical suprarenal tissue have, in a number of cases, in infants and young children, been associated with sexual precocity, and in the case of girls with development of male characters—such as hair on the face.

Many attempts have been made to correlate certain conditions of high blood pressure with hypertrophy of the suprarenals, especially of the medulla; but it is not certain that the suprarenal changes are primary, nor has it been shown that there is an excess of epinephrin in the blood (Stewart).

Osborn, Williams, Sèzary, and others have advanced the view that adrenal deficiency is a causal factor in "neurasthenia," myasthenia, and allied conditions. Modinos has recently advanced the theory that pellagra is similarly due to hypofunction of the adrenals. Some of the disorders of pregnancy (vomiting) are supposed by Zuloaga to be due to adrenal deficiency, despite the usual hypertrophy of the adrenals (cortex) during gestation.

We have referred to the increased sensitiveness of the pupil to epinephrin in certain nervous disorders (dementia precox). But there is no evidence that adrenal hypo- or hyperfunction bears any causal relation to these maladies.

CONTROL OF EXPERIMENTAL ADRENAL DEFICIENCY

Efforts to overcome the effects of the removal of the suprarenals in animals have been made both by the administration of the gland and its

extracts. Neither has met with much success. In no case is life prolonged for more than a few hours after the administration of the gland to animals from whom the suprarenals had been removed. Considerable improvement in the symptoms (increase of blood pressure, improved respiration) has frequently been reported from the subcutaneous or intravenous injection of extracts of the gland, but the results did not differ from those observed in animals near death from poisons and other causes.

So far, transplantation of the suprarenals has been successful only as a preventive measure, that is, it is possible to prevent the characteristic effects of the removal of the glands by the previous transplantation of a gland (Bush). Apparently, when the effects of the removal of the glands have become manifest, it is not possible to delay death by the transplantation of the glands of other animals. Hoskins reports that rats fed on dried adrenal glands for two to nine weeks showed hypertrophy of ovaries and testes, but no change in other organs, in growth or in general condition.

Organotherapeutics in Suprarenal Deficiency in Man.—ADDISON'S DISEASE.—Addison's disease is the only condition in man in which a suprarenal insufficiency clearly exists, and most of the interest in the organotherapeutic use of the suprarenals centers around it. The results are not encouraging.

For the use of suprarenal preparations in Addison's disease, see Vol. III, Sec. IV, Chapter V.

OTHER CONDITIONS OF SUPPOSED SUPRARENAL INSUFFICIENCY.—Suprarenal gland and epinephrin have been administered in a number of conditions in which an insufficiency of the glands had, upon inconclusive evidence, been supposed to be present; the results have been inconclusive.

It has been supposed, for example, that a condition of suprarenal insufficiency exists in many chronic diseases, especially tuberculosis, and the administration of the gland, or of epinephrin, recommended accordingly; Boinet has been especially prominent in the advocacy of this form of treatment. It has also been recommended in certain forms of neurasthenia associated with low blood pressure. It has found a more extensive use in the cardiovascular exhaustion of acute infectious diseases. In this condition, however, it is used as are other cardiovascular tonics, i. e., it is used as are other drugs, and not as an organotherapeutic agent in the usual meaning of this term. Josué claims good results from giving epinephrin or extract of the entire gland by mouth in cases of depressed vascular conditions, assumed to be due to adrenal deficiency.

The suprarenal gland, and especially epinephrin, has been used extensively in osteomalacia. The views as to the value of this mode of treatment (proposed by Bossi) are conflicting; many report favorable results. Novak, for example, reports seven cases treated by subcutaneous injections of 0.5 to 1 c.c. of the one to one thousand solution; three were improved; in two there was a slight diminution of the bone pains at the

beginning; and in two there was no effect. He believes that it should be tried in all cases, and states that no bad effects have been observed, except sometimes slight dizziness and palpitation.

Attempts to deduce a rational basis for the use of suprarenal in osteomalacia have been made from the following facts: There may be some antagonistic (or supplementary) relation between the ovaries and the suprarenals; the latter hypertrophy when the former are removed or are atrophic, and also in pregnancy when parts of the ovary are physiologically quiescent. Christofolletti has advanced the hypothesis that in osteomalacia there is a hypofunctioning of the chromaffin tissue due to a hypofunctioning of the ovaries. As was pointed out above, however, in discussing the relation between suprarenals and the sex glands, the cortex seems to be the part of the former which is chiefly involved, whereas, in the treatment of osteomalacia, a product of the medulla (epinephrin) is usually employed. The favorable results which at times seem to follow the use of epinephrin in osteomalacia are probably due to other factors.

Certain writers have drawn analogies between the skin pigmentation, the lassitude, and the vomiting of pregnancy, and some of the symptoms of Addison's disease, and have treated some cases of vomiting of pregnancy by the administration, *per os* or subcutaneously, of ten drops of the one to one thousand solution of epinephrin; benefit has been reported from such treatment. Epinephrin inhibits the movements of the stomach; possibly it may do the same in pathological conditions from subcutaneous administration.

Eppinger and von Noorden state that the severe diarrhea produced in dogs by the feeding or injection of thyroid can be checked by the administration of epinephrin. They also report that excellent results were obtained in three cases in the diarrhea of Graves' disease from clysmata containing thirty drops of the one to one thousand solution of epinephrin in 300 c.c. of water. They believe that the diarrhea in this condition is due to a stimulation of the vagus nerves, and that this is counteracted by the effect of the epinephrin upon the inhibitory sympathetic nerves. The treatment was successful in the diarrhea of one case of Addison's disease, and they suggest that it may be useful in other forms of nervous diarrhea.

Adrenal preparations have been used in cases of gastro-intestinal atony, in diabetes insipidus, rickets, and other conditions where there is no evidence of primary adrenal insufficiency. Osborne, Williams, Lezari, and others claim good results from feeding or injection of adrenal glands in neurasthenia, myasthenia, and allied disorders.

Other Uses of Suprarenal.—The suprarenal glands and their preparations are used more extensively for the *control of hemorrhage* and as a *cardiovascular stimulant* than for any other purpose; solutions of the active principle (epinephrin) have largely replaced the crude extracts of the glands for this purpose. The use of the drug in these cases does not

differ from that of other pharmacodynamic agents, and its detailed consideration does not properly belong in a chapter on organotherapeutics. The action of the alkaloid, epinephrin, has, however, certain peculiarities which may properly be pointed out in this connection. When applied locally it causes an intense constriction of blood vessels, and this action largely prevents its absorption; hence when given by the mouth or subcutaneously, it produces systemic effects only after very large doses. One hundred times as much is said to be required to produce an effect when given subcutaneously as when given intravenously. Intramuscular injections are much more efficacious than subcutaneous ones.

Epinephrin also differs from most alkaloids (Straub) in that it does not accumulate in the tissues and that it is quickly destroyed in the body; it exerts its action only during its passage into the tissues, and hence its action depends upon the difference in the concentration in the tissues and in the concentration in the blood, rather than upon its absolute amount. Moreover, its effect does not become less after repeated administration; the hundredth injection, for example, causes as great a rise of blood pressure as does the first and subsequent injections.

The above considerations indicate that the best results, when the drug is used as a cardiovascular stimulant, are to be expected from the continuous infusion of a weak solution. This conclusion coincides with clinical experience. Although life has undoubtedly been saved by intramuscular or intravenous injections of comparatively strong solutions (four minims of the one to one thousand solution, for example), the best results have been obtained by the continuous infusion of a solution of one to fifty thousand or one hundred thousand in normal saline solution.

Epinephrin is quickly absorbed from the lungs, and Auer and Gates suggest its administration by intratracheal insufflation in cases calling for a sudden stimulation of the heart.

The use of this drug as a cardiovascular stimulant has proved especially valuable in conditions of cardiac and vasomotor failure under anesthesia (general and spinal), in shock and acute hemorrhage, and in cases of poisoning (as by chloroform and chloral), although very favorable results have also been reported in the low blood pressure of pneumonia and other acute infectious diseases—especially of children. In diphtheria it is said to relieve prostration and asthenia, aside from its effect on blood pressure. [It is valuable in all conditions in which there is vasomotor paralysis.—Editor.] Rolleston administered it by the mouth in ten minim doses of the one to one thousand solution every two to four hours, according to the severity of the attack. Special emphasis has recently been placed upon its value in peritonitis. Thus Heidenhain and Holzbach recommend its administration by continuous infusion previous to operation; they state that a high blood pressure may be maintained in this manner for hours. Heidenhain concludes that if, as a result of the infusion, the

blood pressure is raised and the cyanosis and coldness of the extremities disappear, an operation is permissible; otherwise nothing is of avail. Heidenhain states that the intravenous injection of the undiluted solution, one to one thousand, is not without danger; he considers eight drops of the one to one thousand solution per liter normal saline solution sufficient.

Laewen and Sievers state that in certain conditions of stoppage of the heart the injection of 0.2 c.c. of the one to one thousand solution directly into the heart is permissible.

The greatest field of usefulness of epinephrin, however, is as a *local hemostatic*.

It is used to check epistaxis, and also hemorrhages into the rectum (hemorrhoids), bladder (one hundred c.c. of the one to ten thousand solution, for example), uterus, etc., and to relieve congestion of the conjunctiva and of the mucous membrane of the nose (as in rhinitis and hay fever), and of other organs.

It has been used in post partum hemorrhage; it not only constricts the blood vessels, but causes a contraction of the muscle fibers of the uterus.

It may be applied in solutions of from one to one thousand or one to twenty thousand, either directly or on cotton, or as a spray, or in ointments; cavities, such as those of the nose and uterus, may be packed with gauze wet with a solution one to five thousand or one to ten thousand.

It has also been administered by the mouth (ten to twenty drops of the one to one thousand solution) and also subcutaneously, in gastric and intestinal hemorrhages (as in typhoid fever), although some report but little benefit from such use (Jacobson).

Epinephrin has been extensively used to enhance the action of local anesthetics, such as cocain, novocain, etc. It exerts this action not only by delaying the absorption of the anesthetic (by which the danger of systemic intoxication is also lessened), but, in the case of some of the drugs of this class, it seems to have a direct effect upon the action of the anesthetic itself (Esch). On the other hand, it is stated (Fröhlich and Loewi) that cocain increases the sensitiveness of various organs (blood vessels, urinary bladder, eye) to epinephrin (and to direct stimulation of the sympathetic nerves), so that a weaker solution of epinephrin suffices to cause constriction of vessels when combined with cocain. Such combinations of epinephrin and cocain are useful, not only in cases of operation, but in examinations.

A few drops of epinephrin solution, one to one thousand, are frequently added to Schleich's solutions for local anesthesia; it is also used in connection with the induction of spinal anesthesia.

Epinephrin has been much used to relieve the attacks of bronchial asthma; it is applied locally as a spray (epinephrin one part, water seven hundred and fifty parts, glycerin two hundred and fifty parts (Zuelzer); aqueous solution, one to one thousand or one to four thousand), or as an

ointment (thirty to sixty drops of the one to one thousand solution in *adeps lanæ hydrosus* and *petrolatum*, one dram each), by subcutaneous injection, or by rectal suppository (Matthews).

Clinicians hold widely divergent views as to the value of epinephrin in *pulmonary hemorrhage*; some consider it of much value, whereas others consider it contra-indicated. Attention was called to the fact that experiments on animals showed that epinephrin has little, if any, constricting action upon the pulmonary vessels. Wiggers found that the outflow from the pulmonary vessels was decidedly increased by epinephrin; he considers this due to the distention of these vessels by the augmented contraction of the right ventricle.

The blood vessels of the kidneys and of the intestines are said to be especially sensitive to epinephrin; Wiggers found renal and, under certain conditions, intestinal hemorrhages to be quickly checked by the intravenous or the intramuscular injection of the drug. It has been used with some success in *hemophilia* (Lange).

Preparation and Dosage

The dried powder (*glandulae suprarenales siccae*, U. S. P.) is used chiefly for oral administration; the average dose is four grains. Before the isolation of epinephrin the dried gland was used for the preparation of extracts. Such extracts are efficient, and are far less expensive than the commercial solutions. Among the drawbacks to their use, however, is the fact that they make excellent culture media for bacteria, and it is said that tampons wet with such solutions readily cause infection when left in the nose and other cavities. It has also been shown recently that the commercial preparations of the dry gland vary greatly in activity; Hale and Seidell found some samples of commercial preparations to be seven times as active as others.

At present the drug is employed almost exclusively in the form of solutions of one of the salts, usually the chlorid of epinephrin. The solutions on the market are usually one to one thousand in normal saline solution; they usually contain a preservative. They deteriorate rather rapidly on exposure to air and light, becoming first reddish and then brown; slightly reddish solutions may be used, but the brown ones should not be used. Many of the commercial solutions as found on the market vary greatly in strength (Schultz); this may be due to deterioration through age, or the solutions may not have been made of proper strength originally. They should be physiologically standardized, unless a very pure preparation of the active principle is used.

The active principle of the medulla is known by a great variety of names: *adrenalin*, *adrenin*, *adrin*, *suprarenalin*, *supracapsulin*, *hemisin*, *suprarenin* (both natural and synthetic), *epirenan*, etc. Most of these

names are proprietary. It seems better to use the word epinephrin, proposed by Abel, to designate the active principle.

Untoward Effects.—Considering the extent to which the drug is used, accidents are very rare. A few deaths have been reported from the injection of the one to one thousand solution into veins or into the uterus (Braun, Heidenhain). One milligram injected into a vein has caused alarming symptoms; 0.3 mg. applied to the uterus has caused collapse for one-half hour (Müller).

The intravenous injection of epinephrin is contra-indicated in organic heart lesions, nephritis, and arteriosclerosis (Kauert).

A number of cases of necrosis and gangrene of the skin have been reported following the subcutaneous injection; these occurred for the most part in the aged. Necrosis of the jaw has also been reported.

Severe hemorrhage following its local application has been described; this is attributed to the use of too strong solutions, which constricted larger vessels, so that the surgeon neglected to tie them.

Its repeated administration of large doses to animals is said to cause sclerotic changes in the arteries (Josué). The fact has been disputed; if correct, the sclerosis is probably due to the high blood pressure. Very large doses intravenously are fatal, the symptoms being a primary excitation and subsequent depression and failure of the central nervous system. Post mortem findings are visceral hemorrhages or pulmonary edema (Vincent).

Summary

1. Complete destruction or loss of the adrenal glands is rapidly fatal, but why this leads to death is still unknown. The adrenal cortex appears to be the part of the organ most essential to life.

2. The adrenal medulla secretes a substance, epinephrin, into the blood. In sufficient concentrations this substance has specific and striking physiological actions on the vascular system, the nervous system, the sugar mobilization, and on the blood. But the quantity secreted under normal conditions is not sufficient to produce any of these effects, with the possible exception of some action on the blood capillaries in the nature of controlling their permeability or secretory activity. In conditions of emotional stress and intense muscular and nervous activity there may be enough epinephrin secreted, by secretory nerve action or through change in the blood flow, to have distinct physiological effects—the “emergency” function of the medulla. The medullary secretion has been isolated chemically and shown to be a useful drug in many conditions (shock, circulatory depression, hemorrhage, asthma, etc.) not related to any hypofunction of the gland.

3. The only malady in man so far definitely shown to be due to adrenal hypofunction is Addison's disease. Many other conditions, such

as acute infections, various cachexias, prolonged anesthesia, shock, etc., lead to a great decrease in the epinephrin content of the medulla, apparently due to a primary hypersecretion, but there is no evidence that this is an important factor in these complications. Tumors of the adrenal cortex (hyperfunction?) may be associated with sexual precocity, and there are other indications of interrelation of some of the specific adrenal and specific gonad functions, but this interrelation is not of a compensatory nature, for none of the functions of the gonads can be assumed by the adrenals, or vice versa.

4. Adrenal therapy, fresh gland or extracts, by mouth or injections, have so far failed to maintain the life of adrenalectomized animals. And it has proven itself of uncertain value in Addison's disease. In view of these facts no credence can be given to the reports of good results from adrenal therapy in disorders (neurasthenia, disorders of pregnancy, etc.) where adrenal hypofunction has not even been established. Adrenal organotherapy is therefore still in the experimental stage.

5. In view of the fact that the adrenal medulla and its secretion (epinephrin) appear to be the part least essential to life, experimental and empirical organotherapy of the adrenal glands should be made with the entire gland or with the cortical portion.

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THE SEX GLANDS

THE TESTES

Physiology.—The testicles, at least of the higher vertebrates, contain two distinct types of cellular elements having evidently different func-

tions: (1) the interstitial cells of Leydig; and (2) the spermatogonia, which develop into spermatozoa. The rôle of the spermatogonia and spermatozoa is clear, namely, the fertilization of the female ovum. This fertilization involves two factors on the part of the male element: (1) a stimulus to development of the ovum; and (2) a vehicle of paternal heredity. In performing these functions the spermatozoa act, from the point of view of the male, as an external secretion.

Numerous attempts have been made to isolate the substances in the spermatozoa concerned in these two functions. In the case of some of the lower animals various extracts of the sperms are reported to induce development in the ovum, but there is no evidence that the paternal hereditary factors can be conveyed to the ovum by bathing the ovum in sperm extract.

The cells of Leydig vary greatly as regards relative abundance in the testes of different species. They are quite abundant in man. In animals showing seasonal periodicity in sex activity, the interstitial cells appear to be more abundant during sexual rest than during the period of rut (Tandler and Grosz). The interstitial cells exhibit greater resistance to various agencies. Exposure of the testicle to the x-rays leads to degeneration and atrophy of the spermatogonia before that of the interstitial cells. In testicle transplants, in the condition of cryptorchidism, and after ligation of the vas deferens, the cells of Leydig persist, apparently in normal condition, long after atrophy of the spermatogonia.

Influence of Congenital Absence, Atrophy, or Extirpation of the Testicles.—The effects of castration have been known for a long time through its extensive practice in animal husbandry, and on boys and men for religious and social purposes in various countries. Removal of the testicles in the young vertebrate male has the following effects:

1. It prevents the development of all the secondary male characters (penis, prostate gland, beard, male larynx, male skeletal characters, skin and feather colors, horns, etc.). In some of the invertebrates the castration has no effect on the body male characters.

2. It delays the ossification of the long bones, and the union of sutures of the skull.

3. It leads to certain changes in the ductless glands, the most notable being the enlargement of the hypophysis, and the adrenal cortex, and the retarded involution of the thymus. The growth of the thyroid is said to be diminished.

4. The rate of metabolism is somewhat lowered, with a tendency to adiposity; vasomotor irritability (sympathetic system) is decreased considerably.

5. The most notable mental change in the castrated male is absence of boldness, pugnacity, and viciousness of the normal male, particularly during the breeding season. In this respect the castrated male may be

said to resemble the child or the female. This comparison must not be carried too far. Hikmet and Regnault say of the eunuchs of Constantinople, that "they are avaricious, stupid, credulous, illogical, and obstinate, fanatical, fond of children and animals, faithful in these affections but lacking in courage." But the reader will admit that this characterization will fit many a man with intact and normal testicles.

6. There is no development of the sex urge in the various manifestations.

When the testes are removed in the adult male the most notable changes induced are:

1. Loss of sex urge.
2. Tendency to atrophy of the secondary male characters.
3. Lowered rate of metabolism and tendency to obesity.

The striking specificity of the influence of the testes on organs is shown in the case of the growth of horns.

Horns are modified skin structures apparently identical in all mammals having these organs. Nevertheless in species where the horns constitute a specific male character, castration prevents their development, while in the species where the horns are common to both sexes castration has no effect on their growth.

Thus we see that atrophy or extirpation of the testes leads to impairment and final loss of all structures and functions specific for the sex life of the male, but it does not bring on any serious disturbance of other functions. There are no sequelae comparable to those of the artificial menopause in women. There is no evidence that castration shortens the span of life or measurably impairs the individual's physical and mental efficiency. Senescence in the male is therefore not a direct consequence of hypofunction of the testicles but the result of age impairment of all the tissues.

On the basis of extensive studies on the effects of gonadectomy in the rat Hatai concludes that "the partial removal of the sex glands does not produce any significant alterations in any of the ductless glands aside from a general tendency to a slight increase. Apparently this increase in the remaining gland is sufficient to compensate for the functions of the lost gland."

"The total removal of sex glands, however, induces alterations in all the other glands, particularly in the thymus and hypophysis. The supra-

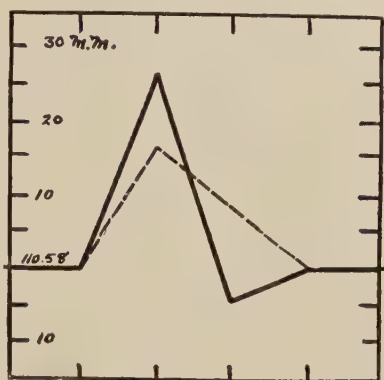


FIG. 24.—COMPOSITE CURVES SHOWING BLOOD PRESSURE RESPONSES TO STANDARD DOSES OF NICOTINE. The continuous line represents reactions before; the broken line after castration of dog. (Wheelon.)

renal glands show opposite reactions in the two sexes. In the case of the males, the suprarenal glands show an increase of 15 per cent., while in the female there is a 20 per cent. reduction."

"The total removal of the sex glands tends to increase the resemblance between the two sexes or, in other words, to reduce the differences in those secondary characters which, in the normal animal, are modified according to sex."

The Function of the Interstitial Cells.—The following facts seem to show that the development and maintenance of the sex life in the vertebrate male is primarily a function of the interstitial cells.

1. In cryptorchidism there may be complete atrophy and absence of spermatozoa and spermatogonia, but if the interstitial cells are present sex structures and functions remain normal.

2. After ligation of the *vas deferens* the spermatogonia suffer gradual and, finally, complete atrophy, but as long as the cells of Leydig are intact sex life remains unimpaired. Extirpation of such modified testes brings on the usual sequelae of castration.

3. Testicular transplants maintain sex life as long as a sufficient quantity of the interstitial cells continues to live, irrespective of the degeneration of the sperm-producing elements, and extirpation of such partially degenerated grafts bring on the typical symptoms of castration.

The control of the sex life of the male by the cells of Leydig is evidently a humoral one, as a denervated testis and a testicular transplant in another organ, and thus outside of its normal sensory nerve relations, function like a normal testis. This is also indicated by the fact that men with complete transverse lesions of the spinal cord, provided the trauma is not great enough to cause marked mental and physical depression from the beginning, retain their inclination toward the female sex, although they can no longer experience the sensations due to erection and coitus.

The Relation of the Interstitial Cells of the Testes to the Cortical Cells of the Adrenals—Hypergenitalism.—From the field of histology and organogenesis evidence has been adduced to show that the cells of Leydig in the testes and the cells of the interrenal or cortical system arise from the same embryological anlage. This may be accepted as true, but it does not constitute a proof that in their adult differentiation the functions of these cells are identical or reciprocal. Instances are also related in the literature of tumors (hyperactivity) of the adrenal cortex producing sexual precocity in boys. This is significant, if true, and if there is no evidence of premature development of the testes themselves. Tumors of the testicles may also induce sexual precocity. However, it is clearly established that no other gland in the body can assume the rôle of the interstitial cells in sex life. After castration in a normal animal the other endocrine glands either remain normal or undergo some hypertrophy. These hypertrophies, even in the case of the adrenal cortex, cannot be of compensatory

nature, at least as regards the specific sex rôle of the testes, since they do not maintain sex life. If the hypertrophies are compensatory it must be in relation to some general metabolic or detoxication function that the testes have in common with other endocrine glands.

Chemistry of the Testes.—The nature of the processes or the substance in the interstitial cells that sustain the male sex life remains unknown. Poehl claims to have isolated a substance from the entire testicle, having the formula $C_5H_{14}N_2$, and called by him *spermin*. He reports that this substance is the physiologically active constituent of testicular extracts, and, injected hypodermically, it accelerates metabolism and acts as a general physiological tonic. Dixon found an abundance of nucleoproteins, other proteins, organic bodies not affected by boiling, and inorganic salts in extracts of the testes. Hernieux reports the presence of lipase and amylase in the interstitial cells. With the possible exception of Poehl's spermin there appears to be nothing specific in these reports. Similar substances are found in all organ extracts.

From a series of very interesting experiments on male frogs Nussbaum concludes that the testicular secretion acts primarily upon the nervous tissue as a tonic or a stimulus, and the augmented or altered activity of the nervous tissue, in turn, sustains the sex life. This view is probably true in specific cases, but cannot be accepted as a complete statement of the situation.

CLINICAL AND EXPERIMENTAL USES OF TESTES EXTRACTS.—1. *Experimental.*—Bouin and Ancel report that injection of testicular extracts into castrated guinea-pigs prevents the atrophy of the male characters. According to the same authors this extract also accelerates the growth of the animals. Loewi states that giving testicular extracts to young capons induces development of the male characters. Walker was unable to prevent the atrophy of the prostate in castrated dogs by injection of testes extracts. C. E. Walker and Riddle have reported that administration of testicular extracts to female animals (chickens, pigeons) tends to produce male characters and male behavior. Meisenheimer states that in castrated male frogs the characteristic development of the forelegs at the breeding season can be induced by testes extracts.

2. *Clinical.*—The testes, variously prepared, was used by the ancient Greeks and the Hindus as an aphrodisiac and tonic. Its modern use in that direction dates back to Brown-Séquard in 1889, who administered extracts of the testes to himself and thought he experienced a great augmentation of bodily and mental vigor. Zoth, and Pregl, using the ergograph, report some evidence of increase in muscular work after subcutaneous injections of the extract. Similar results would probably have followed the injection of any tissue extract. In many of the reports of the action of the extract on normal persons the element of suggestion was not controlled.

The work of Poehl and his associates with spermin was even more sensational than that of Brown-Séquard. Poehl regarded spermin as a general metabolic stimulant or catalyzer and reports good results from its use in the following maladies: Asiatic cholera, syphilis, erysipelas, delirium tremens, gas (CO) poisoning, chloroform and ether poisoning, impairment of heart and lungs, optic atrophy, hemiplegia, paralysis, catatonía, chorea, hysteria, neurasthenia, myelitis, scurvy, marasmus, skin diseases, typhoid fever, toxic goiter, pulmonary tuberculosis, diabetes mellitus, anemia, gout. This is a good example of organotherapy running amuck! There is no evidence that any of these maladies are in any way related to hypofunction of the testes. So far as we know there is no evidence that castration lowers the resistance to infection or otherwise produces conditions favorable to the above diseases. And particularly in cases of toxic goiter, where the destructive metabolism is increased to a degree not found in any other disease, any therapy which still further augments the metabolism is clearly contra-indicated. But others have recommended the use of testicle extracts in toxic goiter, diabetes, obesity, eczema, etc. (Jones, Friedländer, Bauffe, Burghart).

Transplantation of the Testes.—Transplantation of the testes appears to be only a temporary measure, even under the most favorable conditions, as the graft is sooner or later completely absorbed, but as long as a sufficient amount of the tissue remains alive, the graft is able to sustain sex life, even when, as in Nussbaum's experiment, it is placed in the lymph sac. Wheelon and Shipley found that a testes transplant was not able to restore the vasomotor irritability of castrated animals to its normal level, though there was some improvement. Feeding testes was not tried.

Morris has recently reported an instance of a testicle transplant stimulating a dormant testicular remnant so that it hypertrophied into an apparently normal testicle. The patient had lost both testicles at the age of thirteen in a complication of mumps. The man, age 27 at the time of the testicular transplantation, showed the definite effects of complete castration.

Summary

1. The specific sex characters and sex life of the vertebrate male are developed and sustained by hormones secreted by the testes. In the case of the mammals there are indications that some of these hormones begin to function in early embryonic life. The hormones that determine development to full sexual maturity are probably different from those that sustain sex life during full sexual maturity.

2. Complete removal of the testes either in youth or after maturity prevents or abolishes sex life, but has no other significant effect, physical or mental, on the individual.

3. The only fields for rational organotherapy of the male gonads are

the comparatively rare cases of atrophy, disease, or accidental loss of the testes. The rather meager experimental and clinical data on this point indicate that the administration of testicular extract may partly sustain sex life in these conditions, but this therapy is inferior to transplantation. The effects are largely mental. It cannot, of course, overcome sterility. On the whole organotherapy of the testes, from present indications, is very limited, and of little importance.

OVARIES

Physiology.—The ovaries of the sexually mature female contain the following tissues:

1. Ova in varying stages of maturation.
2. Follicular epithelium and liquor folliculi.
3. Corpora lutea, or yellow bodies, developed from the stroma.

In the ovaries of some species a fourth element, or interstitial cells similar to those of the testes, have been described, but these do not form such a distinct element of the ovaries and are more readily destroyed by the x-ray than are the cells of Leydig in the testes.

The corpora lutea are not present in the ovary before puberty. This particular element can therefore play no rôle in the development of the anatomical and physiological characters peculiar to the female sex. This function falls on the follicular epithelium and the stroma.

The Influences of Congenital Absence, Atrophy and Extirpation of the Ovaries.—If the ovaries are removed in the young female the development of all the secondary sex characters is arrested. The uterus and fallopian tubes, the mammary glands, and the external genitalia remain infantile. Heat or rut, and, in the primates, menstruation, do not occur. It is claimed that there is a tendency to development of some of the male physical and mental characteristics. The metabolism is lowered, and there is a tendency to adiposity, just as in the castrated male. Stotzenburg reports that complete ovariectomy in the very young rat accelerates the rate of growth, at least during the first year. Spaying seems to induce less changes in other ductless glands than castration, and, strange to say, in some cases these changes are of the opposite character. Thus ovariectomy in the rat leads to decrease in the size of adrenals, while castration causes adrenal hypertrophy. In the domesticated white rat (normal) the adrenals and the hypophysis are larger than in the male rat (Hatai). The significance of this is not apparent.

Ovariectomy in the adult and sexually mature female leads to atrophy of the anatomical sex characters of the female, suppression of all sex functions and sex behaviors and, in women, to some of the mental and physical symptoms of the natural menopause, such as nervous and circulatory disorders. The persistence of menstruation in women after sup-

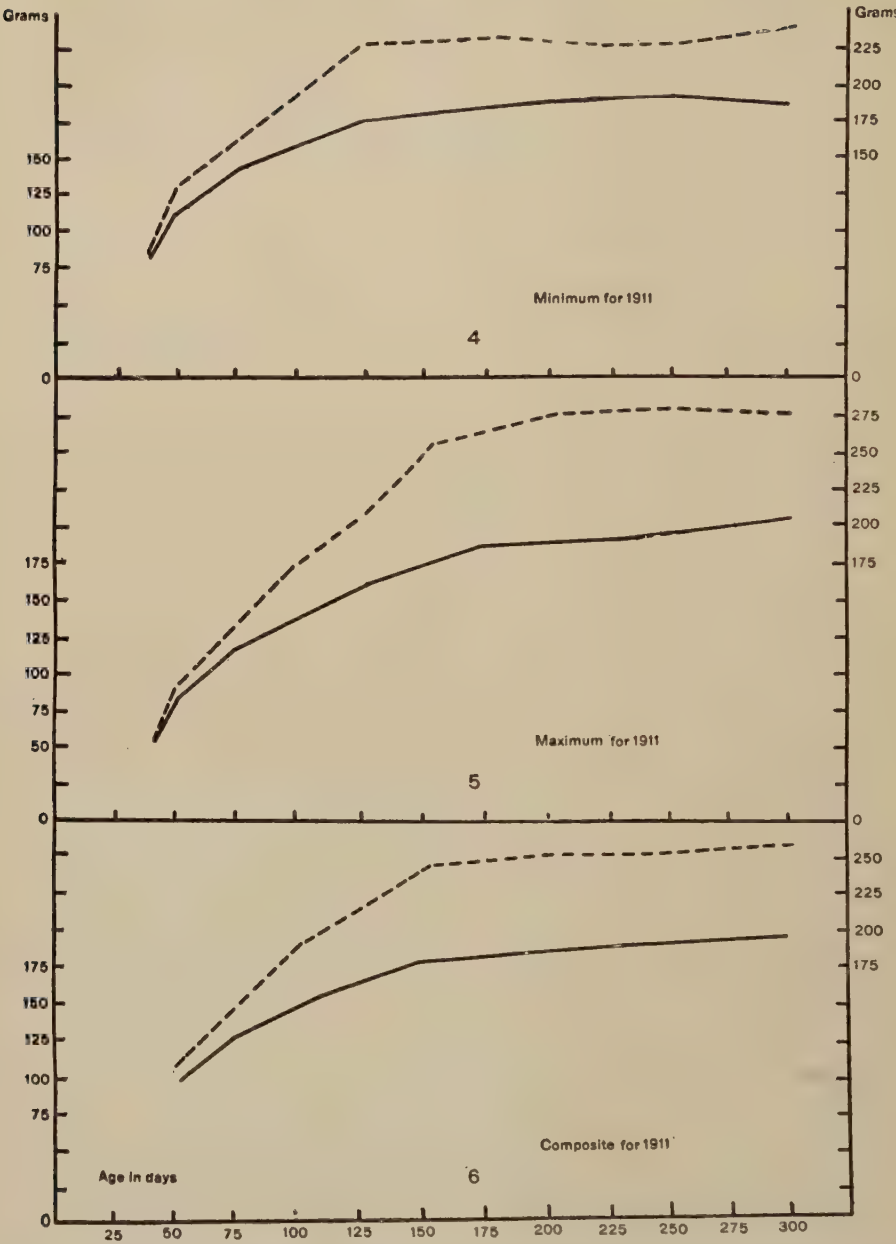


FIG. 25.—EFFECT OF SPAYING ON GROWTH IN THE WHITE RAT. Solid line represents control; broken line represents spayed rats of same litter. (Hatai.)

posedly complete surgical ovariectomy is obviously due to ovarian remnants. This is all the more evident since the clinical literature contains instances of pregnancy occurring after complete ovariectomy, which, of course, is

absolutely impossible. In adult bitches ovariectomy leads to a heightened excitability of the sympathetic nervous system (Hoskins and Wheelon); this may be the condition that causes the nervous and circulatory disturbances of the artificial menopause in women.

Ovarian Transplantation.—1. *Experimental.*—In all species so far tried the ovaries may be successfully removed from their normal position to other parts of the body and continue to maintain their normal function for considerable periods. Transplantation from one individual to another of the same species appears to yield only a temporary success, although Steinach reports grafting of ovaries into castrated males, and testes into spayed female guinea-pigs, the transplants living and functioning long enough to develop female behavior in the original males and male behavior in the original females. Marshall and Jolly, working on rats, found that the transplanted ovarian tissue exhibited all the histological features of normal ovarian tissue, except that the germinal epithelium was invariably absorbed after a short time. In some cases other degenerative changes took place. The stroma might remain normal, while all the follicles had disappeared, or the greater part of the graft might be composed of luteal tissue alone. A point of great importance, noted by these investigators, is that the ovarian transplant undergoes the same cyclic changes as the normal ovaries. In animals killed shortly before the breeding season, large follicles were found in the graft, while a little later corpora lutea were present, showing that ovulation had occurred in the transplant. In one case a homoplastic ovarian graft was found healthy after fourteen months. The longest time noted for a heterotransplanted ovary was six months. Halban reports successful ovarian transplantation in experiments with monkeys.

On the whole the results of all workers in this field agree. The ovarian transplant, as long as it lives, maintains all the functions of the ovaries in their normal position. These functions are therefore hormone or internal secretion processes, that is, primarily humoral, not nervous reflexes.

2. *Clinical.*—Ovarian transplantation, homo- and heterotransplantation, in women has been resorted to extensively in recent years, mainly to control the artificial menopause symptoms due to ovariectomy or to atrophied or diseased ovaries (Morris, Glass, Dudley, Kramer, Tuffier,

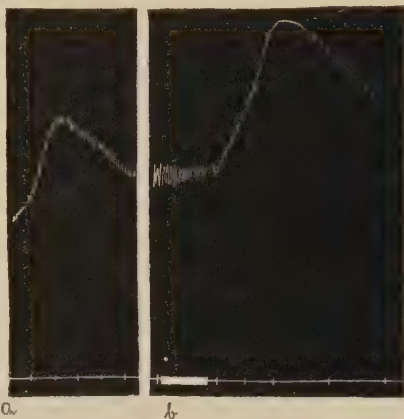


FIG. 26.—RECORD OF DOG SHOWING REACTION TO 0.5 C.C. NICOTIN (1:2000 DILUTION), *a*, BEFORE, AND *b*, 46 DAYS AFTER EXTIRPATION OF THE OVARIES. Blood pressure from femoral artery. Time, 5 seconds. (Hoskins.)

Martin, and others). Clinical results have not been as uniformly successful as those on experimental animals, probably for these reasons: (1) In many instances the ovarian graft was not normal to start with (infection, etc.). (2) In other cases the state of health and nutritive condition of the women receiving the graft were below par—and this militates against a successful “take.” (3) Many surgeons have made the mistake of transplanting an entire ovary instead of one or more small pieces of it. The entire ovary is so large that there will be autolysis and complete destruction of most of the transplanted organ before blood vessels have had time to grow in to maintain its life.

As in the experimental work, autografts have proven more useful than heterotransplants. But Martin notes that either type of transplant may undergo cystic degeneration. So long as a sufficient quantity of ovarian tissue remains the transplant is able to sustain normal sex life, including menstruation. But, at the best, ovarian transplantation for clinical purposes is so far only a temporary expedient.

The Ovaries and Osteomalacia.—The recent reports of favorable effects on the course of osteomalacia from extirpation of the ovaries raise the question of ovarian hyper- or dysfunction. No other ductless gland is known to undergo as great variations in the degree of activity as the ovary—particularly in animals that breed only once a year or only once in their lives, like some species of fish and many of the invertebrates. And yet the hypertrophy and overactivity of the ovaries at the breeding season as compared to the anestrus period induces no symptoms of disease. Even in women adolescence is physiological, and serious untoward manifestations are due to abnormal complications.

The theory that a hyperactivity or perverted activity of the ovaries is casually related to osteomalacia appears to be supported by the recent work of an anonymous German investigator. He claims that an implantation (heterotransplant) of a number of rabbits' ovaries into rabbits produces *experimental osteomalacia* by increasing the excretion of calcium salts and otherwise interfering with the metabolism of calcium. This appears to confirm the earlier findings of Neumann and Vas on effects of injections of ovarian extracts on calcium and phosphorus metabolism. He states that the favorable effects from epinephrin in osteomalacia is due to an inhibitory action of epinephrin on the ovaries.

The Chemistry of Ovarian Extracts.—The ovary produces, in all probability, several hormones, but none of them has so far been isolated and chemically defined or detected in the blood, although Youatt claims that cows can be brought on rut by artificially feeding them milk from cows in rut. F. R. Lillie has shown that the mature ova of certain invertebrates secrete a substance which acts on the sperm to render it capable of penetrating and fertilizing the ovum. In the absence of this substance union of ovum and sperm does not take place. This substance thus ap-

pears to act like the opsonins in phagocytosis. The substance is named *fertilizin* by Dr. Lillie. It can be extracted from the ripe ova by various means, and thus shows some stability. It is likely that similar fertilizins play a rôle in the processes of union of sperm and ovum in the vertebrate, including man, but this hormone or secretion is obviously not concerned in the development and maintenance of sex life, as ripe ova are not present before adolescence, and after adolescence they are present only at definite periods.

Hermann reports that he has isolated a pentaminphosphatid from the corpus luteum. He claims that injection of this substance into animals caused hyperemia of the uterus.

Seitz, Wintz, and Fingerhut report that they have isolated two physiologically active substances from the corpus luteum: (1) a "luteolipoid," and (2) "lipoprotein," or lecithalbumin, called "lipamin." They state that the injection of the latter into animals stimulates the growth of the genitalia, while its injection into women suffering from amenorrhea induces menstruation. The luteolipoid, on the other hand, is said to decrease the menses, and therefore be useful in menorrhagia, especially the excessive menstruation of puberty. We may remark that these two bodies were not chemically isolated and identified, and the clinical findings are not conclusive. For example, the amount of the menses is not accurately determined. According to the theory proposed by Seitz, Wintz, and Fingerhut normal menstruation is a function of the proper balance of the "luteolipoid" and the "lipamin" secretions of the corpus luteum. This seems untenable for the following reasons: (1) These substances were prepared from the corpora lutea of animals that do not menstruate. (2) In women menstruation is usually suppressed by pregnancy despite the persistence and great development of the corpus luteum of pregnancy. (3) Menstruation (or rut) may precede ovulation and hence may precede the appearance of corpora lutea.

The Specific Rôle of the Corpus Luteum.—The sex life of the mature mammalian female is much more complex than that of the male. These are associated with ovulation, gestation, and the nursing of the newly born. A very complicated situation is the absence of menstruation in all mammals below the primates, the relative scantiness of menstruation in all primates below man, and the apparently serious symptoms associated with amenorrhea as well as menorrhagia in women. It is possible that amenorrhea *per se* may not be serious, but that the symptoms are due to the underlying causes that suppress the menses. Menorrhagia is, of course, serious by itself, in that it may produce anemia. There is no question but that menstruation in women is a function of the mature and normal ovary. Does the fact that menstruation occurs in women, but not in the lower mammals, indicate a fundamental difference in ovarian physiology in the primates? The answer to this question is of fundamental importance to

practical ovarian organotherapy, as the only available material for such therapy are the ovaries of the lower mammals. So far as we know ovarian material from the apes has not been tried clinically.

The corpus luteum is a temporary organ, essentially of the mammalian ovary, and the obvious parallel of this organ with menstruation and pregnancy has naturally directed experimental and clinical attention to this organ as a factor of control in these processes. The work of Fränkel, Marshall, and Loeb appears to have established the following facts:

1. The corpus luteum is necessary for uterine changes involved in the inflammation and early stages of growth of the fertilized ovum. Ovariectomy or destruction of the corpus luteum by cautery in early pregnancy (first few days or weeks, the time varying in different species) invariably terminates the pregnancy. When the corpus luteum is destroyed or the ovaries removed later the course of the pregnancy or the hypertrophy of the mammary gland is not interfered with. This latter statement is also confirmed by clinical results. Ansel and Bouin, and especially Loeb, have shown that these changes in the uterus induced by ovulation and the corpus luteum do not appear to depend on the fertilization of the ovum.

It must be remembered, however, that there is some hypertrophy of the ovarian stroma parallel with the development of the corpus luteum of pregnancy, and from the further fact that the luteal cells are derived from the stroma, there remains the possibility that the stroma cells share in the above rôle of the yellow body in early pregnancy.

2. The corpus luteum appears to delay the maturation of ova, thus preventing ovulation. This is probably not entirely a local action on the ovary, for a well-developed corpus luteum on one ovary appears to be able to inhibit ovulation in the ovary of the opposite side. Pearl and Surface report that administration of corpus luteum to hens causes a temporary inhibition of ovulation.

3. The corpus luteum appears to play a rôle in the hyperplasia of the mammary gland that occurs during pregnancy (Ansel and Bouin, O'Donoghue, Hammond and Marshall, Ott and Scott). It is stated that if the graafian follicle of a virgin rabbit is ruptured by mechanical means so that a corpus luteum is formed, hyperplasia of the mammary glands is produced, and also that administration of corpus luteum to virgin animals induces hyperplasia. But the situation is complicated by the findings of Miss Lane-Clayton and Starling, and of Aschner, that similar injections of fetal and placental extracts into virgins also cause hyperplasia of the mammary gland.

4. Experimental work does not support the view of Fränkel that the corpus luteum induces or controls estrus, or menstruation, as in some animals, at least the proestrus and estrus uterine hyperemia precedes ovu-

lation and therefore takes place in the absence of corpora lutea in the ovary.

The Mutual Antagonism of the Testicular and the Ovarian Hormones.

—While the sex life, especially of the mammalian female, is more complex than that of the male, the essential nature of the sex urge appears to be the same in both sexes. This would seem to indicate similar or identical sex hormones. The sex urge and the development and maintenance of the secondary sex characters depend on the ovaries and testes, and given the different embryological substrate for the characters it would seem that these might be stimulated to normal development by identical hormones. Recent experimental work does not support this view. The essential hormones of the ovaries and testes appear not only to be different, but mutually antagonistic, and yet they produce, directly or indirectly, the same mental states in male and female.

We have already referred to the work of Steinach, Riddle, and others of producing "maleness" in the female and "femaleness" in the male by changing the gonads, or administration of gonad extracts. But the most significant contribution to this subject has recently been reported by Professor F. R. Lillie. Lillie's work was done on the "free-martin." The term "free-martin" is applied to the female of heterosexual twins of cattle. It is well established that such females are usually barren. Lillie finds that a twin pregnancy in cattle is almost always a result of the fertilization of an ovum from each ovary; development begins separately in each horn of the uterus. The rapidly elongating ova meet and fuse in the small body of the uterus at some time between the 10 mm. and the 20 mm. stage. The blood vessels from each side then anastomose in the connecting part of the chorion; a particularly wide arterial anastomosis develops, so that either fetus can be injected from the other. The arterial circulation of each also overlaps the venous territory of the other, so that a constant interchange of blood takes place. If both are males or both are females no harm results from this; but if one is male and the other female, the reproductive system of the female, especially the ovaries, is largely suppressed, and certain male organs even develop in the female. This is, according to Lillie, unquestionably to be interpreted as a case of hormone action. It is not yet determined whether the invariable result of sterilization of the female at the expense of the male is due to more precocious development of the male hormones, or to a certain natural dominance of male over female hormones.

If these observations and interpretations of Lillie are confirmed and extended to other animals, we have the extraordinary fact of the development of specific gonad hormones before the gonads have undergone any appreciable differentiation. If this shall prove to be the case these hormones can be produced by nothing else than the primitive germ cells.

We have evidence that other endocrine glands (hypophysis, thyroid)

assume functional importance sometimes during intra-uterine life, but the observations of Lillie place the beginning of fetal hormone equilibrium earlier than hitherto thought possible. It also raises the question of the exchange of gonad hormones between the fetal and the maternal blood. The bearing of a male child obviously does not influence the sex life of the mother. Lillie's interpretation is called in question by the condition of true hermaphroditism—ovaries and testes being present in the same individual, or testes being present with the secondary sex character of the female and *vice versa*.

Effects of Administration of Ovarian Extracts.—1. *Experimental.*—

We have seen that complete extirpation of the ovaries leads to atrophy of the uterus, mammary glands, and other sex characters. These are anatomical or objective changes that may be accurately measured. It would therefore seem that it ought not to be difficult to decide whether ovarian administration is capable of preventing or diminishing these effects of ovariectomy. Nevertheless the literature is conflicting. Jentzner and Beutner, and Carmichael and Marshall, state that ovarian administration fails to prevent the atrophy of the uterus. Okinchitz claims, on the other hand, that the uterine atrophy following spaying is prevented by injections of extracts of the entire ovary, by extracts of the follicular tissue, and by extracts of the chorion, but not by extracts of the corpus luteum.

Various toxic effects have been observed from injections of ovarian extracts (e.g., disturbance of calcium and phosphorus metabolism), particularly in pregnant animals. Ssoloviev reports that corpus luteum and ovarian extracts administered subcutaneously to lactating animals cause increased secretion of milk, and at the same time general deleterious effects leading to death of the animals. These injections are said to be non-toxic in non-pregnant and non-lactating animals.

This action of ovarian extract on the mammary gland was also noted by Ott and Scott. Mackenzie showed that it is absent from extracts of ovaries containing no corpus luteum. The substance must therefore be a product of the latter organ. This mammary gland action of corpus luteum extracts is, like that of pituitrin, not a true secretion of milk, but a stimulation of the smooth muscle in the walls of the mammary alveoli, thus expelling the milk which has already been formed (Schäfer).

Itagaki, a pupil of Schäfer, reports that extracts of the hilum (interstitial cells) of the ovary depress the tone and contractions of the uterus. Extracts of the follicular tissue, and the liquor folliculi itself, produce increased tone and stronger contractions of the uterus. Whether these substances are artefacts, or normal products playing a rôle in life, e. g., in the uterine cramps of painful menstruation, is an important practical question that calls for speedy solution.

According to Sack, corpus luteal tissue added to the food of rats tends to produce adiposity.

Fichera states that the enlargement of the hypophysis following spaying is prevented by ovarian feeding.

2. *Clinical.*—At present the use of ovarian preparations as organotherapeutic agents is confined to gynecology, and their detailed discussion properly belongs in special works on this subject. It seems probable, however, that with increasing knowledge of the relations of these glands to other organs of internal secretion they will acquire importance in connection with internal medicine. Thus, the relations of the ovaries to the hypophysis promise to be of practical as well as of theoretical interest. Fichera stated that the hypertrophy of the hypophysis which occurs in animals after removal of the ovaries may be checked by the administration of ovary. Such results suggest that ovary might be of value in cases of dyspituitarism, and Moffitt has reported a case with obscure symptoms suggestive of dyspituitarism which improved markedly under ovarian therapy: the indefinite nervous symptoms disappeared and menstruation became more nearly normal.

The definite condition where ovarian organotherapy should prove useful is the menopause, artificial and physiological, as this condition is clearly due to ovarian hypofunction.

Many writers report very favorable results in such cases. The attacks of giddiness, trembling, palpitation, flushings, sweatings, and other nervous and vasomotor disturbances are reported to be much reduced in number and severity, or to have ceased entirely in some cases. The best results are obtained in cases of postoperative menopause, especially in young women. Relapses frequently occur after stopping the treatment. Many cases have been reported in which the results were negative, and in some of those with improvement suggestion may have been an important element. Various disturbances of the skin (acne, eczema, and prurigo) occurring during the menopause are said to be benefited by ovarian extract.

Excepting the menopause, practically all the disorders of sex life of women may be due to causes other than a primary ovarian deficiency, so that the use of ovarian preparations in all of these conditions is at present largely empirical, both because of the uncertainties of diagnosis and because of the uncertainty as to the kind of ovary or part of ovary indicated. As Marshall has aptly remarked, "it would seem unreasonable to expect to obtain uniform results from the indiscriminate usage of ovaries in different stages of cyclical activity, e. g., ovaries with prominent follicles like those from animals 'on heat,' or ovaries with corpora lutea like those of pregnant animals, or ovaries in a state of relative quiescence like those of anestrus animals." And it must not be forgotten that ovaries of many of the lower animals also differ markedly from those of man, in accordance with the differences in the sex lives. For that reason

ovarian material from the apes should be given a thorough trial. Some of the conditions in which ovarian medication has been tried, with varying degrees of success, are infantilism, amenorrhea, dysmenorrhea, sterility, repeated abortion, hyperemesis, toxemia of pregnancy, pruritus vulvae, deficient milk secretion. Watson recently stated that he has rarely seen any good effects from ovarian extracts in any of these conditions.

In recent years, following the work and theories of Fränkel, the corpus luteum, or extracts of this organ, has largely replaced the extract of the entire ovary in the therapy of female sex disorders. This is unfortunate, as Fränkel's theory is, at least in part, untenable. From extensive studies on the guinea pig Leo Loeb concludes that the presence of a functioning corpus luteum is necessary for certain of the cyclic changes in the uterus, for other uterine changes the absence of the yellow body is necessary, while for still other phases of the cyclic uterine changes other ovarian structures (probably mature follicles rather than the so-called interstitial cells) are required. But practically it may make little difference, as it is not likely that any manufacturer is so careful that all ovarian stroma and follicular tissue is excluded from their luteal preparations.

Clinical experience, however, has not been uniform. Fränkel reports more or less favorable results in disturbances of the menopause, etc.; but the drug had no effect in dysmenorrhea, irregular menstruation, and the intoxications of pregnancy.

Recently it has been especially recommended in cases of amenorrhea and scanty menstruation, and when there are nervous symptoms which may be due to this insufficiency. It is said by some markedly to increase the menstrual flow and to prevent nervous conditions accompanying their functional deficiency.

Krusen states that in so-called ovarian insufficiency improvement usually follows corpus luteum administration if persisted in for a long time. Burnam reports good results from corpus luteum, given by mouth, in menopause, functional amenorrhea in young women, sterility and repeated abortion. Burnam states that corpus luteum does not induce menstruation in the complete absence of the ovaries. This is contradicted by Donnereruther (one case, no control). This author using the corpus luteum of pregnant cows reports uniformly good results in menopause, functional amenorrhea and dysmenorrhea, sterility not due to infection or mechanical defects, hyperemesis in early pregnancy, repeated abortion, neurasthenic symptoms during menstruation, etc. Culbertson reports good results from corpus luteum feeding on the vasomotor disturbances of the menopause.

Other clinicians report negative or indifferent results from corpus luteum therapy in all of these conditions. Dalche states that in dysmenorrhea long continued use of thyroid gives better results than preparations of the ovary. In Fränkel's hands corpus luteum gave results only in menopause cases. Leighton states that a small number of cases of dys-

menorrhœa, presumably due to ovarian hypofunction, are improved by giving corpus luteum, 15-20 grains per day, for a long time. In some instances this medication caused gastro-intestinal disorders, but no other untoward effect.

In view of the fact that so many physicians have reported good results from corpus luteum therapy in the *amenorrhœa of adolescence*, we were struck by the recent paper of Landsberg where he claims to have cured seven cases of *menorrhagia of adolescence* by a corpus luteum preparation. It would thus appear that the very opposite conditions, amenorrhœa and menorrhagia, are both controlled by the same agent, corpus luteum! It is probable that the luteal therapy has no causal relation to the improvement or cure of either condition, as there is no evidence that the yellow body influences menstruation except indirectly through its inhibitory control of ovulation.

METHODS OF ADMINISTRATION.—The ovary (usually of the cow or sow) has been administered by mouth in the fresh and dried state, and in the form of various extracts, both orally and subcutaneously. At present it is used most frequently in the form of the dried powder, in doses of 0.06 to 0.5 gram (one to eight grains) or more, three or more times a day. Many physicians seem to have employed too small doses. As it sometimes causes disturbances of digestion, its use should be interrupted at times. Einhausen recommended gradually increasing the dose to five grams (75 grains) or more per day, and continuing this for some time after an effect is obtained, and then gradually decreasing for a time.

The dried gland is frequently administered in the form of tablets; the designation of the weights of the commercial tablets is as lacking in uniformity as in the case of thyroid tablets.

The dried powdered corpus luteum (also called *lutein*) has been administered in doses of one-half to two grains (0.03 to 0.12) or more three times a day. It has been used in the form of various extracts. Maits used a sterile one per cent. extract of the corpus luteum in normal saline solution injected subcutaneously in doses of ten c.c.

The contradictory results reported in regard to ovarian organotherapy may be due in part to variations in the character of the gland used. No clinical progress can be expected from further use of commercial preparations until methods of chemical and physiological standardization of ovarian products have been worked out and applied.

Summary

1. The ovaries produce several physiologically important substances or hormones, none of which have been isolated and chemically defined. The development and maintenance of the secondary sex characters of the female is clearly a function of the ovarian stroma and possibly the im-

mature follicles. The initiation of estrus or rut is evidently a function of the mature follicles primarily. The corpus luteum is essential for the processes of early stages of pregnancy. It also retards the maturation of other graafian follicles, thus preventing estrus, menstruation, and ovulation during pregnancy. The ovarian hormones thus control, in part, the activity of the ovaries themselves, and the specific sex functions of distant organs such as the uterus, and the mammary glands.

2. The menopause syndrome, natural and artificial, is primarily due to absence of or hypofunction of the ovaries. All other disorders of the sex life of women may be due to complications outside the ovaries. Some of these complications involve other endocrine glands, notably the thyroids, and the hypophysis. In these conditions diagnosis is frequently uncertain, and unless the malady is clearly due to ovarian hypofunction ovarian organotherapy cannot be expected to yield results.

3. In the present state of ovarian physiology the organotherapy of the natural and the artificial menopause should be undertaken with the extract of the entire ovary rather than with corpus luteum preparations, as the rôle of the latter organ concerns some phases of the early stages of pregnancy and suppression of ovulation, while the other ovarian tissues sustain the fundamental processes of sex life.

4. We may reasonably demand that all ovarian products placed on the market for therapeutic purposes be standardized, at least to the following extent, viz.: the species from which the ovaries are obtained, and whether the ovaries come from animals in estrus, anestrus, or in the state of pregnancy.

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THE SPLEEN

Physiology.—The specific functions of the spleen are as yet largely an open question. In the embryo the spleen forms red blood corpuscles, but after birth or in the adult it seems to be concerned, directly or indirectly, with the destruction of erythrocytes. The spleen, like the liver, contains enzymes which convert the nucleins into uric acid. It is definitely established that the spleen takes part in the fixation of antigens and in the production of immune bodies (Luckhardt and Becht). The immune bodies are internal secretions or hormones. But the decrease in the immunity reaction after splenectomy is not great enough to be of practical significance. In fact, splenectomy in mice is said to increase the resistance of these animals to tuberculosis (Lewis and Margot). Specific relations of the spleen to the pancreas and the liver have been suggested by a number of workers. Asher thinks that the spleen yields a kinase or activator to the liver. Lombroso and Manetti report increase in pancreas secretion after splenectomy. It has also been stated that the secretion of pancreatic juice is impaired in the absence of the spleen. There is enlargement of the spleen and other lymphoid tissue in severe infections.

One fact is definitely established: whatever be the functions of the spleen in man and animals these are not specific, for the removal of the spleen does not seriously impair health, nor does it shorten the span of life.

Effects of Splenectomy in Normal Animals and Persons.—This problem has in late years been extensively investigated by Pearce and his collaborators. In the dog splenectomy causes, as a rule, the transformation of the fatty marrow of the long bones into a richly cellular red marrow (Pearce and Pepper). It is not followed by any marked disturbance in nitrogen and fat metabolism or in iron elimination unless followed by severe anemia (Goldschmidt and Pearce). Raw foods, especially meat, diminish the temporary anemia of splenectomy in normal animals. The temporary anemia (2-3 months) is associated with an increased output of iron in the feces, indicating a temporary decrease in the power of the body to conserve the iron of the decomposed hemoglobin, rather than an increased destruction of erythrocytes. The anemia is not due to lack of iron in the body (Pearce, Austin, and Pepper).

Soper reports an increase of the cholesterol of the blood after splenectomy. The reports on the influence of splenectomy on the resistance of the red blood corpuscles to laking are conflicting, but most workers state that splenectomy increases the resistance. According to Donati, splenectomy increases the permeability of the erythrocytes to glucose. Removal of the spleen in mice *increases* their resistance to tuberculosis, and feeding fresh spleen to mice again lowers this resistance (Lewis and Margot).

Administration of Spleen and Spleen Extracts (Experimental).—Danilewsky, Silvestri, and Krumbhaar and Musser state that subcutaneous or intraperitoneal injections of spleen extracts in animals (dogs) cause a sharp rise in the number of erythrocytes and in the percentage of hemoglobin. This rise lasts but one or two days and may be followed by an equally temporary drop of the erythrocytes below the normal number. It is claimed that extracts of other organs, similarly administered, fail to give this effect on the blood. Hence it appears to be specific for the spleen tissue. But others have reported a temporary increase in erythrocytes and leukocytes after administration of tonsil and lymph gland extracts. The injection of the spleen extract has no influence on the resistance of the red cells to hemolysis. In some cases the administration of the spleen extract induced a slight and temporary leukocytosis, but this was also noted in the case of extracts of other organs. Krumbhaar and Musser conclude that the constant increase in red cells in the peripheral circulation after injection of spleen, in view of the tendency to anemia following splenectomy, suggests that "the spleen may normally exert a stimulating effect upon the formation of red cells in the bone marrow."

Feeding spleen or spleen extracts to animals, even over a long period, has no effect on the blood picture, and fails to prevent or diminish the anemia following splenectomy (Krumbhaar and Musser). This is a fact

of great practical importance for possible spleen organotherapy in man, where repeated subcutaneous or intraperitoneal administration of a crude tissue extract is, of course, out of the question. We see that on the basis of well controlled animal experiments we cannot hope to control spleen deficiency or induce specific spleen functions by feeding spleen or spleen preparations.

Flexner has reported various toxic effects from spleen extract administration.

Hyperfunction or Dysfunction of the Spleen in Splenic Anemia, Hemolytic Jaundice, and Hanot's Cirrhosis.—There is some destruction of erythrocytes in the normal spleen, and possibly some degree of control by the spleen of red marrow, blood plasma, and erythrocytes so that the rate of erythrocyte production and hemolysis strike a balance in the normal animal. In splenic anemia and hemolytic jaundice there are usually enlargement of the spleen, a decrease of resistance of the erythrocytes to hemolysis, and an actual increased rate of erythrocyte destruction, as shown by the output of urobilinogen, urobilin, and iron in the feces. McKelvie and Rosenbloom report a case of hemolytic jaundice and splenomegaly with the erythrocytes showing a decreased resistance to hypotonic laking. The suggestion is made that this may be due to a decrease in the cholesterol content of the blood. Robertson states that in pernicious anemia the erythrocytes of the splenic vein show less resistance to laking agents than those of the general circulation. Extracts of the normal spleen have, however, no hemolytic action *in vitro* (Krumbhaar and Musser). This is also true of spleen extracts from pernicious anemia patients (Robertson). Extirpation of the spleen in splenic anemia appears to restore such patients to normal health, either through the absence of the actual hemolysis taking place in the spleen, or to some increased resistance to the erythrocytes to laking agents in the blood itself.

After an examination of all the cases so far reported Miller concludes that "splenectomy is undoubtedly curative." Gerdes does not appear to be so sure of this. But the improvement following splenectomy shows clearly that the hyperfunction or dysfunction of the spleen is the primary cause of these types of anemias.

The Spleen in Pernicious Anemia.—The relation of the spleen function to pernicious anemia is less definitely established. Most observers agree that splenectomy in pernicious anemia usually induces a temporary stimulation of the blood-forming organs, and hence a transient improvement of the anemic conditions, but "in no case can it be said that the splenectomy produces a cure of the disease" (Krumbhaar). Blood transfusion has a similar stimulating action, but less marked and somewhat more transitory (McClure, Lee, Minot and Vincent). There is, then, no evidence that the spleen functions are primarily concerned in pernicious anemia.

There is no satisfactory explanation of the opposite effects on the blood of splenectomy in normal persons and animals (*temporary anemia*) and in patients with pernicious anemia (*temporary improvement of the blood*).

Therapeutic Uses of Spleen and Spleen Extracts.—The use of spleen extracts in constipation and intestinal stasis as a specific stimulant to gastro-intestinal movements (Zuelzer) is referred to in the section on *Duodenal Mucosa*.

Spleen extracts have also been used in anemia and chlorosis, in malaria, in menorrhagia, and in hemophilia. No reliance can be placed on the favorable results sometimes noted in these maladies, in view of recent work on the relation of spleen to anemia, and the further fact that spleen and spleen extracts given by mouth have no specific action on the organism. The anemias that are benefited by organic iron preparations will, naturally, show improvement on spleen therapy, as the spleen is rich in iron. But this is drug or food therapy, not organotherapy, as this action is not specific for the spleen.

The most strikingly irrational use of any organ or organ extract in therapeutics is that of spleen extract in tuberculosis. Bayle, Harrower, and others have advocated and claimed to have proved that feeding spleen is a *specific* in tuberculosis! There is no basis for such therapy of tuberculosis either in the physiology and pathology of the spleen, or in the biology of the tubercle bacillus. As a matter of fact, Lewis and Margot state that splenectomy in mice increases the resistance to tuberculosis, while feeding spleen has the opposite effect.

Summary

There is, at present, no rational or useful organotherapy of the spleen. Subcutaneous or intraperitoneal administration of spleen extract in normal animals has a transient, stimulating action on the blood-forming organs. There is no evidence (indeed the evidence points to the contrary) that administration of spleen extract has this effect in the clinical anemias. But even if it has, there can be no effective spleen opotherapy of the anemias until the physiologically important spleen substances have been prepared in sufficient purity to permit repeated subcutaneous administration, as all adequately controlled work to date shows that feeding spleen is without specific action.

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THE BLOOD

Blood Transfusion.—The normal blood contains all the substances (nutrients, enzymes, hormones, immune bodies, etc.) necessary for the proper functions of all the organs so far as these are exchanged between the tissues. Theoretically it ought to be possible to administer all hormones to a patient by the transfusion of normal blood; but experiments have shown that the hormones (thyroid, pancreas, adrenal, parathyroid) are present in the normal blood in so infinitesimal traces or are so quickly destroyed and used up that blood transfusion in cases of hormone deficiency has proven of no practical value. Another reason for the failure of transfusion as a general hormone therapy is the difficulty of transferring enough of the normal blood to the patient, without previously

draining the patient of the greater part of his own blood, and without endangering the donor. The 300-600 c.c. usually transferred in blood transfusion of adults is a too small percentage of the total blood.

Considering blood as a tissue or organ, *blood transfusion is virtually organ transplantation*. The blood is the ideal organ for transplantation from the aspect of surgical technique, as there are no nervous and vascular connections to be considered, and, in compatible bloods, no destructive enzymes to be eliminated. But from the physiological aspect we can hope for less permanent results from transplantation of blood than in the case of any other organ. The equilibrium of the blood, both as to corpuscles and plasma constituents, is a dynamic, not a static one, and depends on the activity of the other organs. The effects of blood transfusion are therefore necessarily temporary, and the most satisfactory results are obtained in cases of such temporary needs, as in *hemorrhage*, *carbon monoxid poisoning*, etc.

Blood transfusion has also been tried, with no significant results, in various infections, with the idea of transferring immune bodies and active phagocytes to the patient. It has been tried in *hemophilia*, *purpura hemorrhagica*, etc. But the most extensive transfusion therapy so far developed is that of the various *anemias*. Clinical and experimental experience appear to agree that blood transfusion stimulates temporarily the blood-forming organs of the patient or the recipient, even in cases of pernicious anemia, unless the cachexia approaches that of a moribund condition. The transfusion is therefore of value as a temporary, palliative measure, not so much in virtue of the quantity of normal blood transferred as in the fact that this blood actually stimulates the patient's own blood-forming organs to greater activity. In cases where the anemia appears to be due primarily to too rapid destruction of erythrocytes, we may expect blood transfusion to be of less benefit.

Physiology and pathology give us no basis for expecting, and clinical experience has not shown that anemia, except that due to actual mechanical loss of blood, is cured by transfusion, especially where the condition is hereditary or partakes of the nature of malignancy.

The Therapeutic Uses of Leukocytic Extracts.—Hiss, and Hiss and Zinsser, beginning 1908, reported that intraperitoneal or subcutaneous injections of extracts of leukocytes in animals, and subcutaneous injections of the extract in human patients, protect against many infections (pneumococcus, staphylococcus, streptococcus, meningococcus, typhoid, dysentery, and cholera), and in patients hastens the recovery from these infections. Zinsser, McCoy, and Chapin later reported a similar protective action of leukocytic extract against experimental bubonic plague. Floyd and Lucas, and Lambert also report good results from leukocytic extracts in pneumonia and erysipelas. On the other hand, Alexander observed no favorable results in any infection. Williams and Youland

stated recently that leukocytic extracts have no effect on the temperature, the leukocyte count, the condition of the patients, or the course of the disease in lobar pneumonia. Youland obtained practically negative results with the extracts in experimentally induced, acute infections in animals, thus contradicting the original observations of Hiss and Zinsser.

Archibald and Moore report that injections of leukocytic extracts produce a temporary leukocytosis in normal animals and normal persons as well as in patients with infectious diseases. They claim to have obtained good results, and report one case each of lobar pneumonia, cellulitis, puerperal sepsis, emphysema, and erysipelas. The cases reported prove nothing definite as to the value of the extract injections.

Archibald and Moore ascribe the favorable action of leukocytic extracts to the stimulation of leukocytosis. Manwaring supports the view of a direct bactericidal action of the extract. Such bactericidal action can be demonstrated *in vitro*, but it is too slight to be of any significance when a few c.c. of the extract are injected subcutaneously into an adult person. It has also been alleged that leukocytic extracts increase the immunity reaction, and aid the action of specific serums, antitoxins, and vaccines. There is no evidence for this.

The action of leukocytic extracts in infections is probably not specific. It is well known that the injection of any foreign protein or nucleoprotein produces in most cases a temporary fever and leukocytosis. To the extent that these two reactions are of value in infectious diseases, leukocytic extracts, other organ extracts, or still better, simple proteins, are useful. But this is drug action, not organotherapy.

The important rôle in immunity (phagocytosis, production of immune bodies) ascribed to the leukocytes by the late Metchnikoff is probably responsible for the great attention given to leukocytic extracts in infectious diseases. The leukocytes are not important elements in the fixation of antigens and production of immune bodies (Hektoen and Carlson).

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THE MAMMARY GLAND

The mammary gland is an organ found only in the highest group of vertebrates, rudimentary in the male, and in the female active only for a certain period after parturition. It is not likely that an organ so limited in its distribution and activity has itself any important influence on the vital processes of the mammalian female. The important problems in mammary gland physiology are the mechanism of the gestation hyperplasia and the control of the postpartum milk secretion.

There is not much evidence that the mammary gland produces an internal secretion, beyond the fact that, in women, menstruation is usually in abeyance at the height of lactation, but in other mammals heat or estrus appears shortly after parturition. There is, however, some evidence that it contains substances which have effects (probably not specific) upon metabolism and upon other organs. Thus, Hunt reports that when mammary gland is fed to animals, it causes changes in metabolism analogous in certain respects to those caused by thyroid feeding.

Complete removal of the mammary gland in the adult female is not known to produce any but psychic and cosmetic effects. The complete removal of the mammary glands in young females is said to retard sexual maturity (estrus) and the growth of the uterus (Scherbak). But such mutilated females become pregnant and give birth to the young, as under normal conditions.

Injections of mammary gland extracts are said to retard the development of the ovaries and the external genitalia (Schiffmann and Vystavel). According to Adler they inhibit heat and conception, and in gravid animals cause abortion.

According to Osborne, Luncz, and others mammary gland extracts decrease uterine hemorrhages. Several authors (Bell, Fedoroff, Mekertschians, etc.) report the cure of uterine fibromas and myomas by these injections! Sellheim proposes the removal of the mammary gland to cure eclampsia!

Mackenzie claims that the mammary gland contains a true lactagogue or milk producing hormone—this would be of great clinical importance, if true. But Gavin contradicts it squarely, and in the light of Dr. Gaines' work the results of Mackenzie are in all probability erroneous.

There is no rational or useful organotherapy of the mammary gland at present.

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THE KIDNEY

The theory that the kidneys produce a physiologically important internal secretion, in addition to their excretory function, proposed by Brown-Séquard and d'Arsonval in 1893, has been shown repeatedly to be without foundation (Bradford, Suner, Vincent and Sheen, Karsner, Bumker, and Grabfield), but it still finds some adherents (Itakura). It has been claimed that ligation of the ureters does not produce the same effects on the animal as extirpation of the kidneys; and that the removal of the greater part of the kidney substance accelerates metabolism apart from or in the absence of uremia. None of these claims has been substantiated.

Itakura has recently advanced the novel view that the kidneys regulate the concentration of the sugar in the blood by an internal secretion. This is unlikely, in view of the absence of primary renal involvement in diabetes, and the absence of hyperglycemia or reduced power to oxidize sugar in nephritis, except as due to uremia.

Practically all the therapeutic uses of kidney extracts have been related to conditions of impairment of the excretory functions of the kidney. Capitain, Donovan, Formanek and Eiselt, Renaut, and others have reported the cure of nephritis and uremia by feeding kidney or subcutaneous injections of kidney extracts. Others report negative or injurious effects (Lewandowsky, Senator). Kidney extracts have no specific diuretic action; but kidney extracts for kidney organotherapy are still on the market. Jauregg and Bayer (1914) list seven German and one French commercial preparations.

In the light of our present knowledge of kidney functions and kidney pathology, the treatment of uremia and nephritis by kidney extracts is useless, and possibly injurious.

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THE LIVER

The liver plays a very complex rôle in the animal economy: external secretion (bile), detoxication (ammonia, amino-acids, hemoglobin, poisons, etc.), internal secretion (glycogen, fibrinogen, antithrombin, immune bodies, etc.), desaturation of the fats, etc. So far as we know all these processes depend from moment to moment on the living hepatic cells, and there is *stored up* no substance of the nature of hormone in the liver cells. Hence there is no rational basis for liver organotherapy. Nevertheless, extracts of the liver have been administered (by mouth or subcutaneously) in cirrhosis, diabetes, Banti's disease, hemoptysis, purpura, epistaxis, hematemesis, metorrhagia, prurigo, urticaria, snake bite, and possibly other affections! It appears that most of this irrational and certainly useless therapy has been advanced by European clinicians. Good results are reported, of course. It is not worth while to cite this clinical "literature." Jauregg and Bayer (*Lehrbuch der Organotherapie*) listed only two years ago fourteen organotherapeutic liver preparations on the market. Eleven of these were "made in Germany"!

There is, at present, no rational or useful organotherapy of the liver; and because of the nature of the liver functions there is even no hope for the future in this direction. But biochemical research may produce from

the liver substances of biological and clinical importance in the way of drug actions.

THE FETUS AND PLACENTA

Chemical substances or hormones yielded by the growing fetus (and possibly by the placenta) to the maternal blood appear to control the hyperplasia of the mammary gland during pregnancy, even to the point of actual initiation of the milk secretion (Lane-Clayton and Starling, Ashner). This is probably the normal mechanism, although there are cases on record of mammary hyperplasia and milk secretion in adult virgins and even in males. But there is no practical therapeutic application of this fact, as there is no evidence that feeding placenta or fetal extracts will improve the quality or quantity of milk in nursing mothers (Fieux) or develop the breasts in cases where this may be desired for cosmetic reasons. Ashner reports that placental extract causes ovarian hyperemia and uterine congestion; hence he suggests the use of placental extracts in amenorrhea and sterility.

There is, at present, no rational or useful organotherapy of the fetal and placental tissues.

THERAPEUTIC USES OF OTHER ORGAN EXTRACTS

Brain and Spinal Cord.—The treatment of epilepsy, amentia, dementia precox, mania, melancholia, chorea, tetanus, hydrophobia, etc., with extracts of nervous tissue is, in the light of our present knowledge, less rational and about as successful as the principles and practices of Mrs. Eddy. The clinical literature on this therapy is abundant, contradictory, and worthless.

Bone Marrow.—The red marrow of the bones is an essential factor in the production of red corpuscles, and probably in the formation of many of the immune bodies. But there is no evidence that feeding or injections of bone marrow extracts is of any practical value in bone marrow diseases.

Tumors.—Rational basis for the treatment of malignant growths with tumor extracts has been sought in the principles of vaccination, and the "protective ferments" of Abderhalden. The results are unreliable or negative (Schubert, Bauer, Lotzel and Wissley).

Muscle.—Meat is an excellent food in health, and in most cases in disease. But muscle extracts are of no value as organotherapeutic agents.

Lung, Parotid Gland, Tonsils, Lymph Glands, Retina, Iris, Nasal Mucous Membrane, etc.—It is unnecessary to complete the list. Lung, parotid gland, tonsils, lymph glands, retina, iris, nasal mucous membrane, etc., have been used, *in modern medicine*, to cure disease of these tissues.

The impression left on the author's mind by this literature is a mixed emotion of humiliation and indignation.

RÉSUMÉ

A treatise on the general principles of organotherapy today involves, in a large measure, the disagreeable and thankless task of clearing away worthless and obstructing rubbish. We believe that the reader who has had the interest and diligence to follow us through this chapter will agree to this proposition, and we have endeavored to do it on the basis of clinical and experimental facts and biological reasoning.

The sum total of thirty years of clinical and experimental work in organotherapy, the established facts, are few and quickly stated.

In the greater task of pointing out new lines of possible control we have endeavored to steer a middle course between the Scylla of therapeutic nihilism, and the Charybdis of therapeutic credulity. Where it appears to our fellow workers that we have deviated from this course, candid criticism will be appreciated.

CHAPTER IV

HYDROTHERAPY AND BALNEOLOGY

WILLIAM J. M. A. MALONEY

HYDROTHERAPY

Historical Introduction

188. Lines 3-8 *read*:

Water is thus an ideal medium for the application of **cold and heat, electricity and pressure**, owing to the simplicity, precision, and rapidity with which these physical forces can through it be controlled. Its power in combating disease depends almost solely on its property as a medium. Its physiological action, **when a medium**, is essentially that of the physical force which it is conveying.

189. Line 5 *read*:

served. Urea, xanthin, and other decomposition products of **protein**

190. Lines 13-14 *read*:

vessels. The blood is, in consequence, diminished in the **cooled** part, and a concomitant hyperemia is produced in **other** areas.

192. Line 4 *read*:

strength. The shock produced by the cold must not be too severe. **The severity is mitigated by careful regulation of the temperature of the water, by stimulating the skin either with the impact of myriads of gas bubbles produced by aerating the water, or with massage, and by shortening the duration of the bath.**

Line 21 *read*:

activities and thus **heat** tends to act as a general sedative. Also, the direct

Line 22 *add* after "soothing":

The sedative influence of heat is invaluable in abolishing convulsive seizures due to tonic conditions in children. The warm bath is the surest, safest, and simplest sedative for the irritable nervous system of infancy.

The warm bath has now replaced the opiate "strait" jacket, and padded room treatment of excitement in mental disorders in most modern asylums.

Lines 29-30 *read*:

The **effects** of **heat** and of cold on respiration **appear** to be somewhat similar; each **produces** at first a sharp inspiration; next a pause, and

193. Line 14 *add* after "massage":

In addition to its use as a medium for applying physical agents, water is of great service as a solvent. It is the most universal of all solvents, *the* vehicle for the administration of all soluble drugs.

Water is given to remove in solution or in suspension noxious material, not only from the surface of the body, but also from its apertures and the cavities into which these apertures open. The bladder, uterus, rectum, colon, and stomach are all subject to its cleansing action.

Water is introduced within the lymph-vascular circulation through the mouth and rectum; subcutaneously, intraperitoneally, and intravenously, in order to dilute circulating toxins. By making these toxins less concentrated, water makes them less poisonous. It is similarly administered in cases of shock, particularly shock arising from hemorrhage, in order to refill the depleted vascular system and to provide endocardial stimulation to the failing heart. These diluting and refilling actions are especially valuable in septic conditions, such as forms of scurvy, in which toxemia is complicated by profuse hemorrhages from mucous surfaces, and in diseases, such as cholera infantum, in which toxemia coexists with profuse watery alvine discharges.

Water may be so completely contained in a membrane that no leaking nor oozing occurs, and salt may be dissolved in the water to the point of saturation without impairing the containing power of the membrane. But, if a membrane perfectly containing an aqueous solution of salt be placed in contact with a weaker aqueous saline solution, or with water containing no salt, an interchange takes place through the membrane, so that the salt content of the water inside the membrane becomes equal to the salt content of the water outside the membrane. Salt diffuses from the more to the less salty solution, and water, from the less to the more concentrated solution. This diffusion is called osmosis. The more concentrated fluid is said to have the higher osmotic pressure, and the diffusion ceases when the osmotic pressure on both sides of the separating membrane is equal. Osmosis is one of the most important physical processes in life. It is a determinant of the movements of all the body fluids and promotes the distribution and elimination of the contents of these fluids. Water has a lower osmotic pressure than human serum, so, when swallowed, water passes through the membranous bowel into the lymph vascular capillaries. Water containing so much saline in solution, that it is of higher osmotic pressure than the serum, causes diffusion of fluid from the lymph-

vascular capillaries into the bowel lumen. Thus do saline cathartics produce copious watery stools. Just as osmosis occurs between the bowel contents and the contents of the lymph-vascular capillaries so does it occur between the contents of every living cell and the fluid bathing that cell.

The principle of osmosis has been applied by Sir Almroth Wright, the distinguished Irish bacteriologist, to the treatment of septic gunshot wounds. Antiseptics generally are protoplasmic poisons. The best antiseptics are those which are highly destructive to the protoplasm of bacteria and relatively harmless to the healthy human cell.

Antiseptics, however, are almost invariably additional destructive agents menacing the life of the damaged cells in a wound. After careful observation of the unfortunate effect of antiseptics upon wounds arising in modern war, Wright discarded antiseptics in favor of the bland and uniformly beneficent saline solution. Saline solutions wash wounds free from all uncleanness, exudate, débris and surface organisms; dissolve, dilute and disperse toxins, and by osmosis mechanically relieve cells of their diffusible noxious contents. The natural resistance of the tissues is thus greatly reinforced and the optimal conditions for local repair are ensured. The brilliant results already achieved by Wright with this method of treating septic wounds make this new application of hydrotherapy one of the most important advances in surgery of our time.

Line 39 *read*:

plication. At Nauheim stimulation is **enhanced** by the impact of hosts

199. Lines 29-30 *read*:

The Continuous or Hammock Bath.—The ordinary bathtub is **usually too small** for this purpose.

Line 33 *add after* "nates":

If the size of the bathtub be adequate, a hammock bath can be easily improvised at home; opposite one another, along each of the two sides of a large sheet, four to six pieces of stout bandage are stitched. The pieces must be long enough to allow the free ends of any pair to be tied under the bathtub, when the middle of the sheet rests upon the bottom of the tub. After the patient has been placed in the bath, upon the sheet, the corresponding free ends of each pair are pulled until they are so tightened that the part of the body which their section of the sheet supports is made to assume the optimal position for its comfort. Strips of bandage six inches wide may be used and the sheet altogether dispensed with. If the bathtub rests directly on the floor, stout wire should be twisted into S-shaped hooks, one curve of the S hooks on to the side of the bath; to the other curve, which should be within the bath, the supporting bandage is fixed. An India-rubber air ring makes a good head rest for the bather.

Lines 39-40 *read*:

prevent exposure. A wooden board may be placed across the tub to **sup-**

port the blankets, and also to serve as a tray for the patient's meals. The patient may

Line 44 *add* after "year":

The continuous warm bath quiets the mental excitement of the mad—particularly of maniacs who have cold or cyanotic extremities. Its sedative effect upon convulsive movements in children is remarkable. In septic wounds, especially wounds of the bladder and abdomen, it cannot be too highly recommended. In septic wounds of the limbs, arm, foot, or leg local baths are preferable, for in the hammock bath a *B. coli* infection is soon added to the original sepsis. I have never seen this *B. coli* infection assume a menacing form, but it is both unpleasant and undesirable. When a septic wound is complicated by fracture of the bones, continuous irrigation, or frequently renewed saline compresses are usually preferable to baths, for baths necessitate painful and much to be deprecated movement of the broken bones.

201. Line 6 *add* after "measure":

The radiant heat from electric light is utilized to confer temperatures of several hundred degrees. These temperatures can be easily tolerated for some time, provided the part to be heated is dry and is enveloped in wool or other absorbing material so that perspiration may not gather. Suitably swathed, a limb can comfortably endure a temperature of 260° for half an hour. The apparatus made by Dowsing and by Tyrnauer for administering radiant heat is very practical. The ingenious Bergonie has utilized the heat developed by interposing resistance in an electric circuit in such a manner that he can project heat through the tissues, so that it converges upon a desired focus in an organ or structure yet does not burn the skin. This "diathermia" has already proved of great worth. The application of heat generated by electricity will be fully discussed in the section dealing with electricity.

Line 27 *substitute* for "General Summary":

General Observations.—Hydrotherapeutic applications are extremely valuable agents, but if skill, precision, and judgment be not employed in prescribing and in administering them they may cause great injury. General cold applications should never be given in states of collapse or in exhaustion, if the temperature be subnormal, during a chill, or during a hemorrhage. A patient must be warm before he is subjected to general cold. When there is any suspicion of reactive weakness, the reactive capacity of the patient must be carefully trained by gradually lowering the temperature of the water, and by slowly increasing the duration of the bath; meanwhile, mechanical stimulation of the skin through aërating the water or through friction should be employed. However, in the treatment of tuberculosis Aberg advises the giving of cold full baths without preparatory training of the patient. Full baths of high temperature must

be used with great caution. In arteriosclerosis, renal disease, and cerebral hyperemia, during such hot baths cold must be applied to the head to prevent the danger of an excessive flow of blood from the stimulated body surface to the head (Winternitz's "retrograde hypostatic congestion"). My mistakes have occurred in the use of hot baths for comatose children. Even when the greatest gentleness is used, moving the moribund may precipitate death, and the sudden dilatation of the cutaneous capillaries which follows immersion in the warm bath may so reduce the endocardial stimulation, in cases where diarrhea or hemorrhage has depleted the vascular system, as to cause the heart to stop beating. The hydrotherapist has not the protecting secrecy of the operating room. If the end comes while the patient is in a bath, the relatives may consider the sanctity of death profaned before their eyes. So it is always well in cases of extreme exhaustion to use strychnin, transfusion, pituitary extract or other stimulants, before invoking the restorative power of the warm bath.

Local applications of heat or cold have little influence on general conditions, but we find few contra-indications for them. Local heat should not be applied for the aborting of a circumscribed inflammation as it raises the temperature of the diseased part, increases the congestion, and favors pus formation. Local cold, however, is valuable, for it has the contrary effect to heat. As an analgesic either may serve. Cold is usually better in pain from inflammation for it not only diminishes exudation and thus spares the inflamed nerves from pressure, but it has an analgesic effect on the nerves. Heat is very serviceable in pain caused by nerve lesions. Sometimes trial alone can decide which should be used. It must be remembered that severe cold too long applied may impair the vitality of the tissues. A protecting layer of gauze should intervene between ice and the skin and the application should be discontinued for at least fifteen minutes every hour.

Although hydrotherapy may exert not merely a palliative but often even a curative influence, its habitual use may create a pernicious tendency to rely mainly or exclusively upon it. Other forms of therapy—serum, drug, dietetic, psychic, physical, and operative—should have unprejudiced consideration in the mind of the rational physician, so that the patient's rights may be sacrificed neither to therapeutic habit nor to therapeutic bigotry.

202. Line 17 *read:*

stimulation of the cutaneous nerves by means of **cold** waters charged with salts

Line 32 *read:*

slowing of the rate and **the regular rising** of the cardiac rhythm not only enables the heart

Line 36 *read*:

The application of cold to the **precordium** will show the rapidity of an

203. Line 7 *read*:

Heat **cautiously** applied to the **precordium** may stimulate the heart to more forcible,

Line 39 *read*:

to the precordium and **head** are indicated not only to meet the effect of the

Lines 42-44 *read*:

erate duration and temperature, not exceeding 140° F., **when used in arteriosclerosis as a diaphoretic** must be conjoined with cold applied to the precordial region **and head**. The employment of the hot bath, 95°

204. Line 32-33 *read*:

sitz baths of about 85° F. temperature. Hot hip baths **are valuable to relieve pain and to ensure cleanliness and should be given night and morning. After every evacuation of the bowels cleanliness should be attained by cold sponging.**

209. Line 16 *read*:

Warm sitz baths, 90°-96° F., for thirty to sixty minutes, are recom-

211. Lines 34-36 *read*:

ures **should be directed against the causal factor.**

213. Line 9 *read*:

The spastic variety of costiveness requires **relaxation** measures. Warm

Line 43 *read*:

singultus. **Gauze** should intervene between the

215. Line 20 *read*:

Although control of the body temperature is the cardinal aim of hydro-

223. Line 29 *add* after "months.":

Infantile Paralysis.—There exists at present neither a method to cure nor a means to arrest this dread scourge. Treatment, however, may mitigate the symptoms and by thus easing the patient may conserve his strength and enhance his resistance. Lumbar puncture relieves the pressure on the inflamed edematous nerve cells and may withdraw some of the noxious agent; the toxins circulating in the blood and lymph may be diluted by saline infusions or by blood transfusions; both of these measures will be reënforced by warm baths.

Repeated warm baths were formerly used to induce, through sweating, the elimination of the toxins of infantile paralysis. The periodic immersion and removal of the excessively tender victim entailed much suffering. Oppenheim and Wickman advised against this means of inducing diaphoresis and recommended the employment of packs instead. But even the manipulations necessary to apply packs are often intolerable.

Meddlesome therapy in poliomyelitis may be disastrous. The patient *must not be handled*. The most enlightened care is that which ensures to the child the least possible disturbance. There is no means of sheltering the child more efficacious than the *continuous* warm bath properly given. The bath should be a hammock bath and all necessary adjustments for the comfortable suspension of the patient in it should be made before he is moved. With all gentleness, and with as little noise and disturbance as possible, the patient should be lifted up by means of his bed sheet without touching him, should be carefully lowered into his bath and the bed sheet should be left under him. None other than those needed should be present. The bath should contain just enough water to cover him to the neck.

The toxic action and the pressure of the serous and of the cellular exudate first irritate the invaded nerve tissues. Most of the acute symptoms result from the irritation of the motor nerve cells in the anterior horn of the spinal cord. If the irritation continues the nerve cells die and permanent atrophy of the muscle occurs; but the first effect is to increase the tonicity of the muscles innervated from the implicated nerve cells so that involuntary and painful twitching and spasms occur, with exceeding tenderness. The muscular spasm is not only maintained and aggravated, it may even be caused by external stimuli. The hot bath reduces muscular spasm and provides an unchanging, sheltered, sedative environment in which external stimuli are minimized. Once in the hot bath the patient need not be moved, and his exquisitely sensitive nerves are spared the heaviness of bed clothes, and much of the weight of his body. His terror of approach, his agony on movement quickly diminish, and as his muscles relax the troublesome retention of urine spontaneously disappears. So far as sleep, peace, and relief from pain can strengthen his vitality, the warm bath aids him and this aid may suffice to determine a non-fatal issue.

227. Line 5 *read*:

cases, **during** which there should be no massage of the affected parts. In

Line 22 *read*:

carditis be present, the **bath** temperature should not exceed 98° F. at any time

229. Line 34 *read*:

in diabetes and glycosuria; earthy waters, **in** gravel and stone; Creuz-

230. Line 34 *read*:

ers, as conferring upon them at once a certain **desirable** cosmopolitanism.

231. Line 30 *add* after "solution":

The amount of gas which will dissolve in a liter of water varies with the nature of the gas. Fresh water dissolves more gas than salt water, but

the most important factor in the solution of a gas is the pressure of the gas. The most valuable of the gases in balneology is carbonic acid. At 0° C. and 760 mm. pressure, one liter of pure water can absorb 1,713 liters of CO₂; and the solution is saturated. At greater pressure more CO₂ can be dissolved, the solution can be supersaturated. The dissolved gas is invisible and its solution is not sparkling. Heat or agitation or reduction of pressure converts the tranquil solution of carbonic acid gas into a sparkling, bubbling liquid owing to the throwing out of solution of the carbonic acid gas. In comparing the CO₂ contents of various springs it is, for practical purposes, only necessary to ascertain the degree of supersaturation. Anthony, by experiment, determined that the supersaturation was 25 per cent. at Bad Nauheim; 31 per cent. at High Rock Baths, Saratoga; 33 per cent. at Kayaderosseras baths, Saratoga; 38 per cent. at Bad Momburg; 45 per cent. at Bad Kissingen; 50 per cent. at Bruckenaau and 55 per cent. at Lincoln Baths, Saratoga. At the Lincoln Baths, Saratoga, the greatest supersaturation known in balneology is to be found. The efficiency of the Nauheim Bath is largely due to the action of carbonic acid gas bubbles on the skin. This action can be obtained in unequaled degree at Saratoga Springs, New York.

Line 37 *substitute* after "source.":

Springs that have a temperature above the average of the locality in which they occur are called *thermal*. Thermal springs of a temperature between 70° F. and 98° F. are distinguished as *warm*; and those above 98° F. as *hot*. The temperature of the waters at Aix-la-Chapelle is 167° F.; at Carlsbad, 162° F.; at Bath, 120° F. The following list (Hinsdale) gives the location and distribution of the chief thermal springs in the United States:

	Temperature Deg. F.
Lebanon Spring, Columbia Co., New York.....	75
Spring near Carlisle, Perry Co., Pennsylvania.....	72
Rockbridge Baths, Virginia.....	74
Sweet Chalybeate, Alleghany Co., Virginia.....	75
McHenry's Thermal Spring, Scott Co., Virginia.....	68
Healing Springs, Bath Co., Virginia.....	84
Warm Springs, Bath Co., Virginia.....	96.3
Hot Springs, Bath Co., Virginia.....	106
Berkeley Springs, Morgan Co., Virginia.....	74
Sweet Springs, Monroe Co., West Virginia.....	79
New River White Sulphur, Giles Co., West Virginia.....	85
Hot Springs, Buncombe Co., North Carolina.....	92-117
Citadel Green, Charleston, S. C.....	99.5
Warm Springs, Meriwether Co., Georgia.....	70-90
Livingston Spring, Sumter Co., Alabama.....	68
Bailey's Springs, Alabama.....	72-80
Hot Springs, Arkansas.....	46-147
Hot Springs, South Dakota.....	98

	Temperature Deg. F.
Liberty Hot Springs, Colorado.....	140-150
Hot Springs, Canyon City, Colorado.....	162
Hot Sulphur Springs, Middle Park, Colorado.....	110-117
Glenwood Springs, Colorado.....	124
Idaho Springs, Colorado.....	106
Las Vegas Springs, New Mexico.....	110-140
Hudson Hot Springs, New Mexico.....	142
Ojo Caliente, Taos Co., New Mexico.....	90-122

At thermal baths local painful conditions, nerve or joint troubles of gouty or rheumatic origin, are treated.

RADIO-ACTIVITY

The radio-activity of mineral waters arises from the presence of a gas known as the radium emanation. This gas is derived from the radio-active salts contained in the earth where the spring has its source. The emanation is soluble in water, but decomposes continuously at a known rate, and like other gases, is driven out of solution by boiling. Radio-activity is estimated by means of the electroscope or, with greater accuracy, of the fontactoscope of Engler and Sieveking. The result is stated in Maché units (M. U.) but confusion in standardizing the units exists, so the radio-active values of various springs are not easily judged. Shearer in his report upon the radio-activity of Glen Springs states that the Nauheim Spring there contains 68 M. U. per liter and cites from *Radium* (April, 1915) the radio-activity of Hot Springs, Arkansas, as varying between 0.7 and 23.6 M. U.; of Saratoga Springs, 1.08 and 1.04 M. U.; and of Colorado Springs, 0.21 and 10.4 M. U. Semblin, quoted by Hinsdale, estimates that there are 274 M. U. per liter in Magnesia Spring, 214 M. U. in Boiler Spring, 157 M. U. in Hot Sulphur Spring, and 109 M. U. in Swimming Pool Spring at Hot Springs, Virginia. Radio-active mineral waters are used chiefly to accelerate metabolism. Success is said closely to attend them in the treatment of the metabolic toxemias, which cause gouty and rheumatoid states with accompaniments as myositis, neuritis, and arteriosclerosis.

232. Lines 14-15 read:
America.—See list enumerated under “temperature” (p. 231).

233. Line 17 read:
Springs, Pennsylvania; **Saratoga Springs, N. Y.**
Line 31 read:
Springs, and others, Virginia; Sharon Springs, **Saratoga Springs, New York**; Pacific Con-

236. Line 44 add after “take.”:
The physical effects of the impact of gas bubbles upon the skin are utilized in stimulating baths.

237. Line 3 *substitute*:

INDICATIONS FOR, AND CHOICE OF, A SPA

For those who have the habit of excess in work or in pleasure, a periodic visit to a spa is a useful precaution. For others "taking the cure" is an essential part of social routine. For others, again, especially the middle aged in easy circumstances, who seek relief from the tedium of living by intensive devotion to minor ailments, the spa is a refuge to which they retire from the monotony of family and social life, and in which hygienic, dietetic, and medical discipline provides them with an excuse and with an opportunity for cure.

For tardy convalescence the spa is eminently desirable but not always necessary. In many cases, as in chlorosis, change, alone, is needed. The anemic country girl visits a town and quickly improves. The anemic town girl returns rosy from the sea, the moors, or the mountains. The new régime and environment are sufficient to bring about the desired cure. In other cases the chief factors of benefit in the change are fresh air and exercise; for such the locality chosen should have a slight rainfall in order to insure the possibility of outdoor life; the temperature is less important, for appropriate clothing and exercise will maintain the body heat. But the value of warmth in the winter, to those convalescing from painful nervous and rheumatic conditions, and of coolness in the summer, to invalids from hot stuffy towns, is too well known to need emphasis. But when a change is imperative and medical care is still necessary the patient should be sent to a spa. Good sanitation, comfortable quarters, and constant care can there be relied upon. If a special climate be also desired, all climates are available to the fortunate residents of the United States, and there also is a choice of many different kinds of spas at the same latitude.

But the main sphere of the spa is the treatment of chronic diseases. In the metabolic diseases the eliminating channels are cleansed and maintained clean by the ingestion of the mineral waters and by bathing; dietetic discipline is enforced, so auto-intoxication ceases; physical therapy is practiced which, together with the radio-activity of the waters, promotes oxidation. The control of the bulk of the food and the regular emptying of the alimentary canal enables the weak and overstretched muscles of the stomach and bowel to renew their tone. Massage for the feeble and for those in pain; passive movements, regulated either by masseurs or by the ingenious mechanical appliances of Lander; active movements, in the recumbent posture for the weak; walking carefully controlled distances on level surfaces, or—for the stronger—up measured slopes; and finally, gymnastic practice, swimming, tennis, golf and other outdoor sports;—these means strengthen feeble cardiac and vascular muscles, tone the flabby

voluntary muscles and promote the circulatory, digestive and mental processes.

Under suitable treatment by baths, mineral waters, diet, and physical exercises, metabolism is thus quickened; obesity is reduced; deposits diminish around thickened joints and in infiltrated muscles; pain, therefore, is alleviated, movement returns and wasted muscles recover. Diseased kidneys are rested and their work is lightened to their power to function properly.

In cardiovascular diseases such treatment not only may arrest the morbid process, but also may so tone the weakened heart that edema, pain and breathlessness disappear; and then by carefully regulated training the circulatory system may be further strengthened so that even under considerable exertion the heart acts strongly, regularly and without embarrassment.

In chronic diseases of a less hopeful degree spas afford relief from the weariness and monotony of prolonged home treatment. New surroundings, new physicians, new therapeutic measures seldom fail to relieve the depression, and they enhance the vitality of chronic invalids.

There remain a few spas which are merely "bath houses," but the modern spa is in the truest sense a health resort. Spa therapy is not confined to baths, diets, and exercise. Drugs and every measure which can combat disease are utilized, sometimes even to the exclusion of hydrotherapy. Thus, at Clifton Springs, near Rochester, New York, the spa is organized under the able direction of Dr. M. S. Woodbury into departments of internal medicine, neurology, surgery and pathology. Hydrotherapy, balneology, electrotherapy, physical training and industrial therapeutics are all used there as adjuvants to rational treatment. This excellent institution is operated under a trust deed which requires that all receipts in excess of expenses be devoted to improving the institution and to the care of patients at reduced or free rates. In other spas such as Hot Springs, Arkansas, the American Aix-la-Chapelle, and Mount Clemens, Michigan, the main endeavor is to enhance the efficacy of drug treatment of disease. In these last two institutions unrivaled facilities for the treatment of syphilis exist. The administration of mercury by expert rubbers in a careful, systematic and thorough fashion insures, as far as is humanly possible, freedom from the dread sequelae of this disease and mitigates or removes such symptoms as may arise. The absorption and elimination of the mercury is aided by bathing. The treatment is not confined to mercurial injections; salvarsan and other drugs are also used in appropriate cases. Particularly happy results are attained in the nervous manifestations of syphilis in which the physical therapy relieves pain, promotes nutrition and strengthens the musculature while the drug treatment attacks the essential cause of the malady.

All chronic diseases, except few, such as epilepsy and tuberculosis,

whose victims may be undesirable associates for other sufferers, are treated at spas. Some spas, however, because of their situation or because of the character of their waters are traditionally efficacious in the treatment of special diseases. Thus at Krenznach, Woodhall and Kissingen, exudates from chronic endometritis, perimetritis and salpingitis are said to disappear; even fibroids have been alleged to melt before the solvent action of these waters. At Mannheim and at Rheine cardiac and joint sequelae of rheumatic fever are cured; Schlangenbad is especially lauded for the relief of the neuralgia which so often follows influenza and malaria; the obese and the gouty are catered for at Carlsbad and Marienbad; the syphilitic, at Aix-la-Chapelle;—and so forth. This specialization is of great value. Every facility which science has devised for the treatment of the selected disease is provided at the spa. The spa physicians have a vast experience of these special ailments and great skill in their treatment, and the competition for health among the similarly sick at such spas is of considerable therapeutic value. Hence these spas often confer a more rapid, a greater, and a more permanent improvement than home treatment can attain.

American spas are not yet specialized as European spas. At Glen Springs, New York, particular care is given to cardiovascular diseases. The Nauheim spring is rich in calcium chlorid, and its brine is five times more concentrated than that of Bad Nauheim. Springs at Saratoga are so numerous and so diverse in composition that the waters are especially suited for the treatment of many maladies, among which stress is laid upon digestive disorders, chronic rheumatism and sciatica. The excellent work of Dr. Charles G. Anthony in supersaturating the Nauheim baths with carbonic acid gas makes them unequalled. At Virginia Hot Springs, the American Aix-les-Bains, special study is given to metabolic diseases. The hot baths and the genial climate are grateful in myositis, sciatica, neuritis and rheumatoid conditions, and the radio-activity of the waters enhances their value. At these springs there is an excellent installation of Lander apparatus and physical therapy is well organized. White Sulphur Springs, one of the most luminous health resorts in the world, has a splendid climate, and excellent bathing facilities. Waukesha Springs, Wisconsin, is given up to the treatment of severe functional disorders of the nervous system.

War has made European spas inaccessible at present, and the residual hatred among the belligerents will long deprive the German and Austrian spas of much of their cosmopolitan charm. In the meantime the wealth of balneological resources which the United States possesses is slowly being realized by Americans. The authorities have begun to conserve this wealth, the patients to appreciate it. Foreign spas offer no therapeutic facilities which cannot be equally obtained, both more easily and more comfortably, by Americans at home.

Unless the patient's physical state warrants the strain of a journey the suggestion of a spa should not be made. Having determined that a spa is desirable, the physician considers the accessibility of the spa, its climate, its elevation above sea level, the accommodation it provides, the nature of the waters, the bathing, massaging, and other therapeutic facilities, and above all the quality of the medical care available. These considerations determine his choice. In weakly patients a preliminary course of treatment may be necessary at home before any journey is attempted. Thus, in severe heart cases, a modified Nauheim treatment may first be instituted by the private physician; then a home spa may be utilized in order to strengthen the patient for the long, rough journey, or the stormy sea voyage, or the rigors of the new climate, and then the possibly more desirable and efficacious foreign spa is attempted.

241. Line 29 *read*:

then **Glen Springs, Clifton, Saratoga** or some other spa, where cardiac troubles are especially

242. *add* under "References":

Anthony, C. G. Actual Values in the Nauheim Treatment, Modern Hospital, Feb., 1916.

Ferris, Warren. Reduction of Obesity, Med. Record, Jan. 22, 1916.

Hinsdale, Guy. American Thermal Springs, Med. Record, May 1, 1915.

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Lieb, C. W. The Nauheim Treatment as given at the Glen Springs, Can. Practitioner and Review, April, 1916.

Oppenheim. Quoted by Wickman, loc. cit.

Wickman. Acute Poliomyelitis. Authorized Eng. trans. by W. J. M. A. Maloney, New York, 1913, p. 122.

CHAPTER V

THE PRINCIPLES OF MEDICAL CLIMATOLOGY

HENRY SEWALL

247. Line 23 *add* after "medicine." :

It is important to realize that, while man moves and breathes in a gaseous atmosphere, the protoplasmic units of which he is constructed are bathed in lymph which forms his true internal environment the constancy of whose composition is at least as important to normal life as is that of the circumambient air.

When the normal alkalinity of the blood suffers a reduction there is immediate physiological reaction and the disturbance may be so profound as to destroy life. This condition of "acidosis" is the result of obscure and probably diverse causes. It is desired here to express the suspicion that the physiological relations of climate are largely achieved through a modification of metabolism, one of the results of which is an alteration of the acid-alkali balance of the blood. Similar results may follow stimuli as widely different as diet and psychic emotion. It is quite possible that physiological effects which we attribute to climatic change are often directly mediated through such plasma changes, as have been indicated.

259. Line 23 *add* after "occur." :

It seems obvious that lumping of the earth in masses would not only facilitate the development of macroscopic interstices, favoring a run off of water, but would impede the penetration of the clods. On the other hand, pulverization of the soil would both annihilate its drainage channels and set each particle free to exert its maximum absorption on the falling moisture.

266. Line 15 *add* after "solved." :

The writer has found that guinea pigs sensitized by subcutaneous injection of horse serum are, in a large proportion of cases, temporarily de-sensitized by exposure in a horse stable.

267. Line 36 *add* after "rooms.":

Lee and Scott have recently reported experiments in which it was found that in cats, confined for six hours in a ventilated box where temperature and humidity could be regulated at will, the excised muscles at the end of this period showed a loss of work power when the air of the box had been maintained at high temperature and humidity (91° F. and 90 per cent.) as compared with normal conditions. The sugar content of the blood diminished 6 per cent. under the same circumstances.

The present writer has pointed out, as had M. J. Rosenau previously, on the basis of experiments in anaphylaxis, that substantial evidence exists for the absorption by the respiratory tract of protein matter diffused in the air with the result of producing profound changes in cellular irritability. Therefore, any practical view of ventilation which ignores chemical pollution of the air is unscientific and dangerous.

269. Lines 29-34 *read*:

the blood." Haldane, Douglas, Hendersen and Schneider submitted the physiological influences of high altitudes to a searching investigation during a sojourn of 35 days on the top of Pike's Peak, Colorado (elevation 14,000 feet). They conclude that all the vital modifications witnessed at high altitudes are the result of one cause—lowering of the oxygen pressure in the air.

They found "after acclimatization the resting arterial oxygen pressure had risen about 35 mm. of mercury above the alveolar oxygen pressure, whereas, at or near sea-level, the resting arterial oxygen pressure is no higher than the alveolar oxygen pressure. The raising of arterial oxygen pressure is attributable to secretory activity of the cells lining the lung alveoli, and is a most important factor in the acclimatization. On breathing air rich in oxygen, the secretory activity was rapidly diminished." The fundamental significance of this alleged oxygen secretion, coordinated with the respiratory needs of the body, may well hold the attention. It

271. Line 9 *add* after "conditions.":

Haldane and his co-workers made a critical study of the blood as affected by barometric pressure. They found that "the percentage of hemoglobin increased for several weeks on the summit of Pike's Peak and varied in various acclimatized persons from 115 to 154 per cent. The number of red corpuscles increased parallel with the hemoglobin."

Much of the work that has been done in this field is held by Burkner and his associates to suffer from defects in method. These observers maintain that the increase in the red blood count for moderate elevations, up to, say, 10,000 feet, is much less than has usually been asserted.

Abderhalden and others have considered the altitude-polycythemia to be the result, not of increased blood formation, but of blood concentration

from excessive evaporation. Another view assumes that under low barometric pressures there is an unusual accumulation of corpuscles in the peripheral vessels from which estimations are made. The excellent work of Loevenhart and his colleagues seems to have disposed of these doubts as to the existence of a true altitude-polycythemia and the active stimulation of the blood-forming organs through reduction in the partial pressure of oxygen.

Loevenhart confined rabbits in ventilated boxes in which, while the total barometric pressure was kept constant, the proportion of oxygen was widely varied. It was found that, under these conditions, lowering the oxygen tension produced blood changes similar to those realized when a like fall in oxygen pressure was due to elevation above sea-level.

273. Line 22 *add* after "mendations.":

The radiant energy of the sun is undoubtedly a powerful physiological stimulus, capable of working either good or harm to the body. Heliotherapy is in an empirical stage. Such experiences as those of Rollier in the cure of surgical tuberculosis under sunlight deserve critical confirmation. Webb correctly urges the caution in the application of the method.

The writer saw one of his patients who had apparently cured himself of a severe ulcerative tubercular laryngitis by the daily application, for a few minutes, of sunlight to his larynx. The light was reflected by a pair of polished metal mirrors and guided by a laryngoscope. It was presumed that the ultra-violet rays, probably excessive in the Colorado sunlight, were the efficient agent.

274. *add* after table:

In his recent study of the influence of climatic factors on human efficiency in its broadest sense, Prof. Huntington gives the preëminent place to temperature; he writes, "The law of optimum temperature apparently controls the phenomena of life from the lowest activities of protoplasm to the highest activities of the human intellect."

275. Line 19 *add* after "tunnel.":

White and Shuey found it extremely difficult to estimate the morbid influence of smoke in the air of manufacturing centers. They conclude, however, that "there is a general tendency of the tuberculous death-rate to rise as the number of smoky days in the city decreases; there is a general tendency for the number of deaths from pneumonia to fall as the number of smoky days in the city decreases."

It is obvious in estimating the hygienic relations of atmospheric impurities, these should be primarily divided into two groups according to their solubility or insolubility in the body fluids. To the first class, including sulphuric acid, etc., we might perhaps expect relatively acute physiological response. The second class operates slowly through struc-

tural alterations of the lungs manifested as more or less extensive pneumokoniosis.

In a recent, unpublished investigation A. J. Lanza, of the U. S. Public Health Service, has analyzed the data presented by "Miners' Consumption" as it occurs among the workers in the Joplin mines of Missouri. The mines produce lead and zinc and the offending dust is siliceous from powdered flint. Miners' consumption is due to the deposit in the lungs of solid particles, the irritation of which sets up a progressive fibrosis. The early symptoms of the disorder are a gradually increasing dyspnea on exertion, diminished respiratory expansion and pains in the chest. Many of the victims examined had been at work for ten to fifteen years, but it was not uncommon to detect signs of silicosis in those who had worked less than a year in the mines. Sooner or later the subject of miners' consumption is prone to develop either tuberculosis or pyogenic infection of the lungs or both. Out of 720 miners examined by Lanza 433 had miners' consumption and of these 103 showed tubercle bacilli in the sputa. The numerous X-ray pictures of the chest which illustrate this research are strikingly suggestive of the plates obtained in pulmonary tuberculosis of glandular and bronchial type with bilateral distribution of disease. In advanced cases the great masses of shadow, which are visible on the X-ray plates, can be distinguished from those of ordinary tuberculosis only through the lack of signs of cavitation.

280. Line 40 *add* after "thyroid." :

The writer has recently been impressed with the importance of considering the acid-alkali balance of the blood as a factor affecting tissue resistance. Where a condition of acidosis exists, as may be manifested by an excess of acetone in the urine, mysterious disorders may sometimes easily be corrected by the application of appropriate alkaline and dietetic treatment. There is reason to believe that the backsets to which many tubercular invalids are prone without apparent cause often find their explanation in a recurring acidosis.

281. Line 30 *add* after "level." :

The writer has had intimate opportunity of studying the case of a man who in Denver suffers much from ill-defined pains, at times characterized as muscular rheumatism and headaches which are relieved by salicylate of soda. These symptoms disappear on a journey to sea level and remain in abeyance for some weeks after his return.

286. *add* under "References." :

Lee, F. S., and Scott, E. L. Amer. Jour. Physiology, 1916, XL, 486.
Sewall. Interstate Med. Jour., 1916, XXIII, 23.

Haldane, Douglas, Hendersen and Schneider. Phil. Trans. Royal Soc., 1913, CCLIII, 185.

Burker, *et al.* Zeits. f. Biol., 1913, LXI, 379.

- Loevenhart. Arch. of Int. Med., 1915, XV, 1059; also Dallwig, Kolls and Loevenhart, Amer. Jour. Physiol., 1915, XXXIX, 77.
- Rollier. Die Heliotherapie der Tuberkulose, 1913.
- Webb, G. B. Jour. Outdoor Life, 1915, XII, 277.
- Huntington, E. Civilization and Climate, Yale Univ. Press, 1915.
- White and Shuey. Trans. Amer. Clin. Assoc., 1913, XXIX, 233.
- Sewall. Arch. of Int. Med., 1914, XIII, 856.

CHAPTER VIII

ELECTROTHERAPEUTICS

WILLIAM BENHAM SNOW

369. Lines 4-6 *read*:

vantage in the employment of **sinusoidal apparatus, wall plates and direct current motors for static machines.**

Lines 8-9 *read*:

almost indispensable for use in connection with **the above apparatus** for conversion of the alternating into the direct current. The

Line 26 *read*:

to produce thermic effects, which **produce the greater degree of amperage**

370. Line 41 *read*:

view of the three characteristic properties of the **different currents**, afford

374. Line 26 *read*:

The modalities from the static machine, which also **produces a**

375. Lines 15-18 *read*:

cal effects of the static current. There are, **however, several** conditions in which this current excels the other currents in therapeutics. **It is of marked value in the treatment of constipation and in developing atrophied muscles, as in poliomyelitis.**

378. Line 14 *read*:

the affinities to be so strong for the opposite **polarities**, that largely ac-

380. Line 2 *read*:

derstanding of the details of administration, that a full **recognition**

Lines 35-38 *read*:

its volume or quantity. There **may** be, therefore, three or four sizes of terminal balls for operating the current with varying force, according to the conditions treated. **As a rule, however, the terminal ball one inch in diameter is preferred.**

396. Line 7 *read*:

which conducts electrical currents, an **acid or alkaline** solution, always

402. Line 35 *read:*

as **it should be** in all cases when hyperemia is to be maintained in accordance with

404. Line 8 *read:*

X-ray should be made for fully **fifty** minutes with an intensity ap-

407. Line 41 *read:*

phagocytes **envelop** the cocci present.

422. Line 48 *read:*

has been successful in more than **300** cases, and his experience has been confirmed.

431. Line 40 *read:*

More than 25 per cent. of **300** cases of prostatitis that the writer has

CHAPTER IX

RADIANT LIGHT AND HEAT THERAPY

WILLIAM BENHAM SNOW

437. Line 30 *read*:

who understand the principle when living in the tropics, to wear **dark** colored

438. Line 24 *read*:

of **radiant energy** are the radiations from radium, uranium, and other radioactive

439. Line 44 *read*:

of nitrous **oxids** and ozone, which are produced in large quantities by the

440. Line 13 *read*:

combines with the radiant light **the important advantages** of radiant heat.

Line 19 *read*:

upon **a table**. **The high power carbon filament** lamps, applied with the

Line 32 *read*:

power have an emphatic deficiency in heat radiations. **These lamps, however, are so deficient in the lower frequencies, the so-called heat radiations, demonstrated to penetrate, that though intense heat effect may be produced at the surface, the effects on the deeper tissues are not productive of the hyperemia required in conditions of infections and impaired metabolism. Tungsten lamps have, therefore, proved generally disappointing in the hands of those who employ radiant energy with a rational idea of its effects and therapeutic indications.**

441. Line 3 *read*:

connection that radiant heat **production** plays a most important part in
Line 6 *substitute*:

THE KROMAIER LAMP.—The Kromaier lamp is constructed on the Cooper Hewitt mercury vapor principle and provided with windows of rock crystal for transmitting the ultra-violet radiations. These lamps

possess special merit in therapeutics for the treatment of telangiectasis, rosacea and angioma, as shown by Dr. Wm. L. Clark of Philadelphia. The administrations are made with the part affected firmly compressed beneath the rock crystal lens. By first covering the marginal tissues with adhesive plaster, the reaction is confined to the affected tissues. Exposures, according to Clark, should be made for approximately 20 minutes, and repeated after ten days if necessary.

442. Lines 23-38 *read*:

tion. **A carbon filament lamp** of this type has been manufactured, in which the lamp is so placed with reference to the parabolic reflector that parallel rays are projected. **A lamp of this kind** may be suspended over an affected part at the distance at which it can be tolerated for the time necessary—usually, for one hour, as for treating otitis media, acute coryza, erysipelas, boils, carbuncles, or other local infections.

Various types of construction of lamps of high candle power are now on the market. The tungsten filament lamps have proved to be a disappointment, demonstrating the greater therapeutic value of the lower frequencies of radiant energy as obtained from the carbon filament incandescent lamps.

443. Lines 39-43 *read*:

ing 200° F. in the bath. **It is doubtful if, as previously stated,** the luminous effects of these lights add to the therapeutic value of the radiant light bath.

Mirrors and reflecting surfaces within the light bath are of little if any practical value; **for it has been demonstrated that it** is not even

449. Line 13 *read*:

lupus was the first to arouse an interest in **phototherapy** and its possibilities

450. Line 27 *read*:

tinued for at least one **full** hour, and will, as a rule, result in the abortion

452. Line 7 *read*:

rence whatever of the affection during the past **two years**. This case

453. Line 17 *read*:

should should be used **together with** administrations of the **X-ray**,

CHAPTER X

RADIUM THERAPY

WILLIAM HENRY BEAUFORT AIKINS

461. Lines 19-22 (B. F.). Lines 16-19 (F.) *read:*
sources are carnotite and pitchblende or uranium oxid, found in various parts of the world. Carnotite is a uranyl vanadate of potassium occurring in extensive deposits in Colorado and Utah, and in smaller deposits of very low grade in other localities, as, for example, in Pennsylvania. Pitchblende is found chiefly at Joachimsthal in Bohemia, but it is also found in Hungary, Saxony, Turkey, Cornwall and Sweden.

Line 32 (B. F.). Line 29 (F.) *read:*
But pitchblende and carnotite are not the only source of radium. Small quantities

Line 35 (B. F.). Line 32 (F.) *read:*
minerals also contain small traces of radium. It is found to occur, also in

462. Line 10 (B. F.). Line 9 (F.) *read:*
by separating it into ions. 4. Its production of certain rays which can
Line 16 *read:*

The radiation given off by radium is complex and has been found to
Line 21 *read:*
particles of matter, about four times the mass of an atom of hydrogen. They

Lines 33-34 *read:*
projected with a velocity almost as great as that of light. In mass they are about 1-1700 of that of the hydrogen atom, and in all respects except

Line 44 to **463.** Line 1 *read:*
radiation. They have great penetrating power, requiring ten centimeters of lead for their nearly complete absorption. They have a velocity equal to that

463. Line 18 *read:*

Radium Emanation.—In addition to the radiation, radium gives off energy in

464. Line 17 *add* after "etc.":

When large quantities of radium are used it is also desirable to screen the radium tube with two or three millimeters of rubber, paper or gauze to cut off the Sagnac rays and prevent undesirable secondary B ray effects.

465. Line 12 *add* after "diseases.":

Owing to the action of the radiation on the varnish, the life of these applicators is comparatively short, those having the greater amount of radium per unit area, being the shorter lived.

A new type of flat applicator has recently been developed in which the radium salt is fused to the metal back in a smooth glaze or enamel. This type of plaque may be sterilized and cleansed as any metal or glass object would be, and has the advantage over the varnish plaques of lasting much longer.

466. Lines 6-17 *read*:

factor to be considered in directing the treatment. It is now usually measured by the amount of radium salt per unit area. Following the suggestion of the London Radium Institute a unit of concentration has been adopted. "This consists of a centigram of radium bromid spread over a square centimeter. Applicators containing radium salts to this extent of concentration are said to be "full strength" applicators; similarly half and quarter strength applicators contain respectively 0.5 and 0.25 centigrams of radium bromid to each square centigram." On this continent it has come to be accepted that the quantity of radium is best expressed in terms of radium element. Thus pure hydrous radium bromid contains 58.6 per cent. of radium element; pure radium sulphate contains 70.2 per cent. radium element; pure radium chlorid contains 76.1 per cent. and pure radium carbonate 79.0 per cent. of radium element. In accordance with the practice of the London Radium Institute, a "full strength" applicator contains 5.36 milligrams of radium element per square centigram of area. With the apparatus as purchased one

467. Line 8 (B. F.). Line 9 (F.) *read*:

is **ten** to **one hundred** micrograms of radium. Five to ten injections are given

468. Line 28 *read*:

After exposure to a varnish apparatus of **quarter strength** for ten applica-

470. Line 36 *read*:

Mills. An apparatus of **quarter strength** activity was used, so screened as to

471. Line 9 to **473.** Line 1 (inclusive) *substitute*:

Radium in Internal Medicine

A large amount of clinical work has been done in recent years to establish the pharmacological action of radium emanation, and the indications for its employment therapeutically. It has been found that radio-active water given *per os* is absorbed by the intestine and reaches the blood stream. A large portion is deposited in the bone marrow where the radio-activity persists from several days to several weeks. It is excreted in the urine and feces. On the blood picture there is first an increase followed by a decrease of leukocytes, while the red cells are permanently increased. Blood pressure is gradually reduced. The blood viscosity is markedly lowered. Its action on ferments is interesting. The gastric, pancreatic, glycolytic, diastatic and other ferments are accelerated so that metabolism in general is increased. There is increased diuresis, while on the nervous system a sedative effect is noticed. While certain observers have reported the changes noted above, further carefully controlled chemical observation should be made, to verify them, before the use of radium emanations can be accepted as justified.

Therapeutically in arthritis deformans, gout and rheumatism radio-active water has been most frequently used, the beneficial results being first observed by Gottlieb among the miners working among the pitchblende at the radium mine in Joachimsthal. The use of artificially radio-active waters in arthritis, gout and rheumatism has not shown uniform beneficial effects in the hands of unprejudiced clinicians.

In arteriosclerosis radium taken internally has been said to have a markedly beneficial action, this being due not only to its lowering blood pressure, but probably also to a favorable effect on the internal secretions.

473. Lines 25-33 *substitute*:

The methods of administration of radium internally are numerous. Many of the natural mineral waters, famed as curative in the conditions mentioned above, have been found to be radio-active, and the inference has been drawn that the benefits derived from bathing in and drinking these waters have been due to their radium content present as radium emanation, which is a gas and soon passes off after the water is removed from its source.

By the addition of radium in small quantities to indifferent waters they may be made therapeutically active, and can be transported and made use of at any time. Such products are on the market containing one or two or more micrograms of radium to each bottle, this giving a corresponding number of microcuries of radium emanation.

When immediate use is to be made of the radio-active water, it may be prepared by passing into it a definite amount of radium emanation, obtained from a supply of radium in solution. Various forms of ap-

paratus for thus preparing emanation water are to be obtained, but caution must be exercised in their purchase, and no type should be used which does not produce at least two microcuries of emanation per day in the drinking water.

474. Lines 32-42 (B. F.). Lines 20-30 (F.) *substitute*:

Eczema.—As it has been demonstrated that radium has an action on the sensory, motor and trophic functions of the nervous systems, it is obvious that it ought to exert a beneficial effect in eczema which is characterized by trophic and sensory disturbances. As a rule of course it has only been in obstinate cases that radium has been employed with the result that relief has been experienced after all other methods have failed. In chronic dry eczema great success has followed the application for short periods of plaques or toiles of a low degree of radio-activity, the intolerable itching being usually relieved within a short time after beginning treatment. Wickham and Degrais report favorable results in about two hundred cases thus treated. Bayet reports 41 successful cases out of 42 treated. The London Radium Institute reports favorably on the use of radium in the treatment of lichenification of the skin.

In acute eczemas with a tendency to recurrence the applications of unscreened plaques for five minutes are very useful, repeated if necessary. It is advisable in treating eczema with radium not to neglect ordinary local and constitutional measures.

Line 43-44 (B. F.). Lines 31-32 (F.) *read*:

In the case illustrated an apparatus of large surface and **of quarter strength** was used, with a very feeble filtration. The apparatus

479. Line 3 (B. F.) *add* after "satisfactory." **476.** Line 10 (F.) *add* after "days":

Tuberculosis of the Skin.—The destructive action of radium is of great service in the healing of tuberculous diseases of the skin other than lupus vulgaris. In verrucose necrogenica, the so-called post mortem wart in chronic tuberculous ulceration, in scrofuloderma, radium used in sufficient strength to create a well-marked reaction causes a destruction of the diseased tissues, followed by healing with a smooth non-disfiguring scar.

Lines 22-25 (B. F.). **477.** Lines 2-5 (F.) *read*:
have been obtained with plaques **of one-quarter strength (British measurement), screened with 1-10 mm. of aluminum.** Each individual case must be experimented with at first

481. Line 15 (B. F.). **478.** Line 39 (F.) *add* after "methods.":

Telangiectases.—Telangiectases either of natural development or produced as a result of irritation of the skin by electric needles, the X-ray,

etc., may be treated by the application of radium in the same way as an ordinary nevus, and with excellent effect in causing the disappearance of the dilated capillaries.

Pigmented Mole.—The destructive action of radium is most useful in effecting the removal of these disfiguring growths. One must use sufficient exposure to produce a rather severe reaction, which causes the abnormal tissues to disappear, their place being taken by a smooth, non-pigmented scar. One case in particular the writer can think of where, in a young girl, the right cheek was the site of a hairy black mole, elevated above the surrounding skin. By means of radium practically all trace of the disfigurement has been removed, and with the aid of cosmetics the former location of the mark is barely noticeable.

Line 30 (B. F.) *add* after “radium.”:

Synovial Lesions of the Skin.—This rare condition which shows itself as warty or pseudovesicular projections from the skin over the sites of bursae connected with tendons was first described by Jones and Makins, of London, as very refractory to treatment.

The writer has found, in two cases he has seen, that radiumization sufficient to cause good reaction results in the disappearance of the lesions. This observation has been confirmed by Sutton of Kansas City.

482. Line 3 (B. F.). 476. Line 38 (F.) *add* after “treatment.”:

The more recent the development, and the younger the subject the better the prognosis, so that one should not countenance delay in treatment, even in the case of very young children. Pain which is so marked in many keloidal developments is easily relieved by the anesthetic action of the radium rays.

As instancing the difference in effect between radium and the X-ray in such conditions, the writer has had one case of successful removal of a keloid, which had been caused by the healing of an X-ray burn.

Lines 22-29 (B. F.) *substitute*:

Since then many others have made use of the action of radium rays in diminishing vascularity to treat cases of Graves' disease, and their reports all agree that in radium a most valuable accessory agent in the treatment of conditions of this disease is at our service.

It has been pointed out that the great advantage radium possesses over the X-ray is the fact that the treatment can be given without noise or excitement in the quiet of the patient's own room and that the dosage may be accurately regulated.

Certainly in the writer's experience treatment by radium has been a complete success, and patients who received no benefit from all other recognized forms of therapy have been entirely restored to health. From the commencement of the treatment, patients have shown relief from the nervous and pressure symptoms with diminishing of the size of the gland.

Well screened quarter-strength plaques should be used, and long exposures of one hundred hours or more given in order to obtain proper results.

Simple Adenomatous Goiter.—In many cases of simple adenoma of the thyroid gland marked shrinking, if not complete retrogression, of the tumor may be brought about by the application of radium.

This is a method of procedure of which more use should be made than is commonly done in the large number of cases in which, for one reason or another, surgical interference is contra-indicated.

483. Lines 3-11 (B. F.). 479. Lines 30-36 (F.) *read*:
field of usefulness in gynecological conditions.

Of the non-malignant conditions the one in which most work has been done is that of fibroid of the uterus. Here the hemostatic action of radium has a distinct field of usefulness, and the menorrhagia and metrorrhagia which almost invariably accompany the growth are soon relieved, together with a marked reduction or complete disappearance of the tumor mass and the relief of pressure symptoms.

The immense importance of being able to effect cures by measures other than operative is only just beginning to be appreciated, but the increasing number of reports confirming the almost selective action of radium upon uterine fibromata leads me to the conclusion that radi-umization will soon be the method of election in the treatment of this condition.

Other conditions met with in gynecological practice such as pruritus vulvae, urethral caruncle, vaginal polypi, chronic metritis, are most favorably influenced by the use of radium.

484. Line 22 (B. F.) 480. Line 44 (F.) *add* after "surgeon.":

Military Surgery

Radium in Military Surgery.—The present European war has brought many new problems to the medical profession. One of the most pressing is the problem of securing quickly the healing of the severe infected and contused wounds met with in thousands among the casualties.

An opportunity having been afforded for an investigation into the effects of radium on subacute wounds, certain results well worthy of attention were obtained, which will be of value either in military or civil practice.

It was established that stimulating doses of radium rays (ten to thirty-five milligrams of radium element in tubes from ten to twenty minutes) were most effective in causing the healing of long-standing wounds, while destructive doses caused much aid in the removal of sloughs.

The effect seems to be brought about by a stimulation of the leukocytes, thus increasing the patient's resistance and enabling him to overcome the persistent chronic infective organism.

Lines 23 to 485. Line 16 (inclusive) (B. F.). 481. Lines 1-35 (F.) *substitute*:

Epithelioma of the Skin.—Under this heading one must consider the basal celled epithelioma—the so-called “rodent ulcer,” and the squamous-celled epithelioma.

The rodent ulcer is more amenable to treatment by radium than any other form of malignancy, and it was from the effects of radium in these lesions that stimulation was given for research on the effects of radium in other forms of malignancy.

When Wickham first reported his results in the treatment of rodent ulcer he spoke of a “selective” action of the radium rays in these cases. It is true that by relatively short exposures healing can be effected with practically no visible reaction, but the writer has noticed, and the report of the London Radium Institute confirms it, that cases treated in this way show a tendency to break down again. As a result one would advise heavy destructive doses in order that no doubt may exist that the total of the involved area has been completely destroyed. Using a plaque of quarter strength, an exposure of 8 to 12 hours may be given over the affected tissues. This will result in a fairly severe reaction, but when healed there is much less likelihood of recurrence. The scar formed is from a cosmetic standpoint most satisfactory, being smooth, non-depressed, and in a short time hardly distinguishable from the normal skin.

As a rule one heavy exposure of the type mentioned is sufficient, but cases will arise in which further exposures may be necessary to receive the desired result. These should hardly be repeated at less than five to six weeks' interval, as the radium reaction takes this length of time to subside.

Prognosis should always be guarded where rodent ulceration has extended so as to involve bone or cartilage, as healing does not occur with the same readiness. Neither should too prolonged exposure be given as the reaction is apt to be particularly severe. In these cases it is well to screen the plaques with aluminum, 1/10 mm., so as to avoid undue reaction.

485. Line 31 to 486. Line 22 (inclusive) (B. F.). 482. Lines 8-31 (F.) *substitute*:

Squamous-celled Epithelioma.—Heavy radiation gives excellent results in this condition, but it must be emphasized that insufficient dosage may result in stimulation of the growth. When little ulceration is present, an exposure of twelve hours to a plaque of one-quarter strength is usually sufficient. If there is much thickening and involvement of surrounding

tissues, longer exposures with plaques screened either with lead or aluminum, for from 24 to 60 or more hours, should be used. In this way the harder "ultra penetrating" rays are employed. The "cross-fire" method, too, may often be used with advantage, if the type of lesion is one that offers itself readily to this method of attack. Frequently in this condition there is considerable fungation of the growth. A preliminary curetting followed by heavy radiation of the base hastens the time of repair.

487. Line 3 (B. F.). **483.** Line 10 (F.) *add* after "used.":

One must mention here the importance of watching closely the adjacent glands in all lesions of this type. Frequently after all trace of the primary growth has disappeared, secondary deposits may be found in the glands. Occasionally, too, an ulcer proved histologically to be rodent will give rise to squamous-celled cancer in the adjacent glands. When such involvement is detected surgical removal is indicated with subsequent heavy and prolonged radiation of the gland-bearing area.

Lines 40-44 to **488.** Lines 1-2 (B. F.). **484.** Lines 18-24 (F.) *read*: to the use of radium. Best results have been obtained by **using heavy destructive doses with an unscreened plaque of quarter strength for eight to twelve hours.** Wickham and Bayet have both reported favorable results.

When metastases have developed in the cervical glands, the latter should, if at all possible, be removed surgically. Subsequently, a heavy exposure to the more penetrating rays over the area of operation distinctly lessens the possibility of recurrence.

488. Lines 3-10 (B. F.). **484.** Lines 25-32 (F.) *substitute*:

Cancer of the Tongue.—In epithelioma of the tongue the use of radium fails to give the desired result. Of late a method of using the emanation has led to more optimism, however. This consists in the burying in the carcinomatous nodule of a small but very powerfully radioactive emanation tube, screened by one millimeter of silver, and left in situ for 24 hours. Naturally, this results in a severe reaction, but in the reported cases a certain number have ceased to grow, and have been replaced by firm fibrous tissue.

In certain pre-cancerous conditions such as leukoplakia, indolent ulceration, often associated with a syphilitic history, the use of radium sufficient to cause a moderately severe reaction has been most effective in restoring the normal appearance.

Line 27 (B. F.). **485.** Line 5 (F.) *add* after "later.":

In the treatment of the small subcutaneous nodules which so often develop along the line of incision after operation for excision of the breast, radium is an invaluable agent. Screened plaques will cause their complete disappearance.

Line 28 to **489.** Line 5 (B. F.). **485.** Lines 6-27 (F.) *substitute*:

Cancer of the Uterus.—All radium therapists are agreed that radium has made a distinct place for itself in the treatment of cancer of the uterus. There are three definite indications for its employment. 1. In inoperable cases. 2. After operation as a prophylactic against recurrence. 3. In the treatment of the small recurring nodules that are apt to develop in the vaginal walls.

In inoperable cases the local manifestations of malignancy are materially and strikingly affected. Fungating vegetations, ulceration, hemorrhage, foul discharge, pain, may be made to completely disappear. The tendency to form metastases is also distinctly lessened.

After hysterectomy radiation of the vaginal vault, undoubtedly, checks recurrence in the scar, while in the treatment of the isolated recurring nodules which so frequently develop in the vaginal walls, radium is definitely indicated.

The treatment may be given by tubes or plaques; frequently a combination is useful to produce "cross-fire," the tube being passed per vaginam against or into the cervix, held in place by a tampon, while a plaque is applied on the vaginal wall. Massive doses are well borne as a rule except where, after panhysterectomy, there is so much interference with the trophic nerves that it is well to give about half the usual exposure, in order that severe ulceration may be avoided.

489. Line 9 (B. F.). **485.** Line 31 (F.) *add* after "variety.": Although it is claimed by one observer that if growing tissues other than bone, the spindle-celled sarcomata respond to the action of radium with as satisfactory results as do the round-celled.

490. Line 18 (B. F.). **486.** Line 27 (F.) *add* after "other.":

Endothelioma.—Endothelial cells appear to be particularly sensitive to radium, so that one is not surprised to learn that endothelial tumors are favorably influenced by the radium rays. Where operable, they should of course be removed, but the writer has found that postoperative radiation decreases the liability of recurrences, while recurrences that have developed may be checked and made to disappear.

Details of treatment do not differ from those employed in other forms of malignant growth. Either plaques or tubes or both may be used.

491. Line 15 (B. F.) *add* after "symptoms.":

The writer, from an experience of several cases of this condition, can endorse these observations. Patients to whom a most unfavorable prognosis had been given, have lived in comfort, and further development of the growth apparently arrested.

Cancer of the Bladder.—In inoperable carcinoma of the bladder a certain success has attended the use of radium. In two cases treated with benefit the hematuria, cystitis and subjective symptoms disappeared, while on examining with the cystoscope a diminution of the growth in size and the cover of its ulcerated surface with healthy epithelium was seen.

The radium is applied by means of a tube fastened in a catheter with a window directed against the growth. "Cross-fire" may be secured by placing other tubes in the vagina or rectum of the base if the bladder is involved or on the anterior abdominal wall should the growth be on the anterior vesical wall.

Cancer of the Rectum.—The indications for the use of radium in this condition are very similar to those for its use in carcinoma uteri. In inoperable cases, preferably after a preliminary colostomy, the introduction of a radium tube per anum against the mass results in shrinkage and fibrosis of the malignant growth, so much so that subsequently surgical removal of the mass may be effected. The object of the colostomy is to prevent the irritation of fecal matter over the involved portion of the bowel.

"Cross-fire" may be obtained by a well screened plaque smiting hard Beta and Gamma rays, and applied over the sacrum.

492. Line 19 (B. F.). 488. Line 22 (F.) *add* after "use.":

It is becoming increasingly recognized by the surgeon that radium gives him an auxiliary of which formerly he stood much in need, in his dealing with malignant disease. It lessens the chances of recurrence after operation, it gives invaluable aid as a palliative agent in the treatment of the inoperable cases, so that from a source whence at one time disparaging remarks regarding the efficiency of radium were wont to come, come now the reports of the beneficial effects of this agent. One thing, however, must be emphasized if proper results are to be obtained—sufficient dosage of radium must be used. Men who are employing small quantities expecting to get proper results will be disappointed. Not only so, but they are doing a great injustice to their patients, and to the science of Radium Therapeutics.

CHAPTER XI

X-RAY THERAPY

SIDNEY LANGE

495. Line 44 (B. F.) **491.** Line 44 (F.) *add* after "polarized.": It can, however, be diffracted.

Röntgen in his original monograph stated that the X-ray could not be diffracted. Artificial diffraction gratings are too coarse to disperse the X-ray bundle. Recent experiments have shown that by utilizing a certain quartz, whose molecular structure presents a four-fold symmetry, the X-ray bundle can be dispersed. The molecular interspaces of the quartz furnish a natural diffraction grating.

The practical observations that the X-ray may vary in its composition or quality and may, therefore, produce varying effects, are thus scientifically proved.

509. Line 44 to **511.** Line 40 (inclusive) (B. F.). **505.** Line 44 to **507.** Line 40 (F.) *substitute*:

The recent invention of a new type of X-ray tube termed the Coolidge tube (after its inventor) has given a tremendous impetus to X-ray therapy. This tube differs markedly from the original type of X-ray tube both in the physics of its operation and in the biological effects of the rays which it emits. The introduction of this new tube has at once given us a more efficient and more powerful source of X-rays and has made possible the achievement of results which were hitherto unattainable.

The Coolidge tube has a vacuum of perhaps a few hundredths of a micron and the internal pressure is perhaps less than one hundredth part of the pressure in the usual type of tube. Owing to the almost complete absence of gaseous particles there are no positive ions present in the excited tube and therefore there is no fluorescence of the glass walls of the tube and no heating of the active hemisphere. In order to liberate the electrons which constitute the cathode stream, the cathode is heated by means of an independent insulated twelve-volt current. The number of electrons liberated depends upon the temperature of the cathode, hence

the amount of current which can be passed through the tube and the intensity of the X-radiations emitted are governed entirely by varying the temperature of the cathode. The heat generation occurs almost entirely at the target which, being composed of a solid block of tungsten, can withstand high temperatures. The heating of the target does not influence in any way the intensity or penetrating power of the rays emitted. The quality or penetrating power of the rays emitted from the Coolidge tube is dependent entirely upon the voltage at the tube terminals which may be varied at will. As it is possible to maintain a voltage of 90,000 to 100,000 at the tube terminals it is possible to produce rays many times as penetrating as those emitted from the older type of tube. The hardest rays from the Coolidge tube are far above the range of the usual types of penetrometers and approach in hardness the lower gamma rays of radium. Because of the method of control the Coolidge tube will produce either hard or soft rays at will in a practically homogeneous bundle and over an unlimited period without alteration.

The Coolidge tube is, therefore, an instrument which approaches the ideal requirements for Roentgen therapy. It generates a constant homogeneous bundle of X-rays of any desired hardness and intensity which can be varied at the will of the operator independently of each other. In contradistinction to the Coolidge tube which is practically gas-free the older types of X-ray tubes are usually referred to as "gas" tubes. The discharge current in the Coolidge tube is purely thermionic in character. The Coolidge tube is by far the most efficient type of tube for all kinds of X-ray therapy. It is especially adapted to deep therapy because of the great penetrating power of the rays which it may generate and because of the fact that it can be operated constantly for hours without altering in any way the quantity and quality of the rays emitted.

A great many full doses of deep irradiation can be administered in a short period of time, permitting of utilization of the cross-fire method to the fullest degree. In administering deep therapy with the Coolidge tube the skin should be protected with an aluminum filter at least three millimeters thick. The secondary rays given off by the aluminum filter should be absorbed by a heavy piece of leather placed between the filter and the patient. As the bundle of rays approaches homogeneity the tube can be placed close to the skin if a filter is used and the voltage of the tube terminals is high. The heavy aluminum filter will be sufficient to remove most of the comparatively few soft rays to be found in the hard bundle.

The clinical results obtained by the fullest utilization of the Coolidge tube cross-fire deep irradiation have been far more satisfactory than those obtained by the use of the gas tube. Indeed the introduction of the Coolidge tube advanced radiotherapy appreciably towards its goal.

In the course of deep filtered Coolidge treatments the skin may exhibit a peculiar reaction. There may be an erythema followed by an exfoliation

of the superficial layers of the epidermis leaving a weeping surface. If the rays have been well filtered the reaction does not go beyond this stage. The lesion tends to heal readily without scarring. This process is quite different from the so-called Roentgen dermatitis in that it is very superficial, not painful (unless irritated by clothing, etc.) and heals readily. The term epidermitis has been given to this reaction. It is similar to the reaction produced by radium, thus emphasizing the analogy between the hard Coolidge ray and the gamma ray.

Such a reaction is best treated by exposure to the air and the use of an alkaline watery lotion, preferably lime water. Bandages, salves, and ointments tend to delay healing. The contact of the clothing acts likewise by adhering to the lesions and pulling off the crusts.

The administration of the multiple deep doses by the cross-fire method produces a toxemia far more severe than that observed following gas tube therapy. This may take the form of malaise and headache or there may be vomiting, weakness and prostration. These symptoms may be so severe as to influence the prognosis and may prevent efficient irradiation of the lesion.

The toxemia may be allayed or prevented by forced ventilation of the treatment room, by blowing fresh air over the patient or by drawing the gases generated about the X-ray tube out of the room. There are reasons, however, for believing the toxemia is the result of a post-irradiation acidosis, and the most satisfactory results may be obtained in many cases by the administration of alkalis before and after each treatment.

555. Line 30 to **556.** Line 42 (inclusive) (B. F.). **551.** Line 30 to **552.** Line 42 (F.) *substitute*:

Goiter.—Deep filtered irradiation of the thyroid has produced excellent results in a surprisingly large percentage of cases. The discouraging literature of the past which was based upon gas tube irradiation is being rewritten. If the treatment is carried out boldly and persistently, using the Coolidge tube and the cross-fire method, the percentage of failures will be as low as that obtained under the surgical methods of treatment.

Primarily the X-ray method has been regarded as a method of last resort in those cases in which operation is contra-indicated or refused. It can well be regarded as worthy of an early trial. The rationale of the treatment is based upon the fact that the X-ray inhibits the activity and causes atrophy of glandular structures. It follows, therefore, that the parenchymatous types with simple hypertrophy of the secreting tissue are more favorably influenced than the fibroid, colloid, and cystic types. The changes resulting from the X-ray therapy consist in a fibrous degeneration and encapsulation of the gland and are necessarily slow in developing. At least three months' time should elapse before drawing conclusions as to the results of the treatment.

While X-ray therapy will diminish the size of the gland, its power of diminishing the internal secretion of the gland is often of overshadowing importance. This is especially true in the so-called exophthalmic types and in the larger group of border-line cases which present more or less definite signs or symptoms of thyroid intoxication. This latter type of thyroid disturbance yields most satisfactorily to X-ray therapy. The muscular pains, headaches, nervousness and many allied symptoms rapidly disappear under the proper X-ray therapy.

The well defined type of thyroid disturbance known as exophthalmic goiter, varies in its response to X-ray therapy with its chronicity. The early and incipient cases of exophthalmic goiter will respond more quickly and more satisfactorily than the long established cases with myocardial and other complications. Some improvement can be expected in every case providing the irradiation is sufficient in amount and a sufficient time is allowed for the fibrosis to take place. The nervousness and tremor improves first, then the tachycardia and finally the exophthalmos, although the latter symptom is the most difficult one to influence. Complete disappearance of a well marked and long-established exophthalmos is not common, although a varying degree of improvement is the rule.

The technique consists in cross-firing at the gland, giving as many doses and at such frequent intervals as the integrity of the skin and the systemic condition of the patient will permit. Ordinarily, two full doses given once a week for five weeks will suffice. To safeguard the skin, they should be administered alternately to front and back of neck one week and to the lateral surfaces of the neck the next. Some of the treatments should be given low enough to include the thymus gland, which is often enlarged and plays some part in the toxic types of goiter. If the toxic symptoms are severe, the treatment should be undertaken very cautiously, as temporary exacerbation of symptoms may follow heavy treatments.

Prostatic Enlargements.—The application of X-ray therapy to prostatic enlargements often produces the most satisfactory results. Before the introduction of the Coolidge tube it was quite difficult to satisfactorily irradiate the prostate because of its deep position and the inefficiency of the gas tube. Cross-fire irradiation, using the most penetrating rays from the Coolidge tube, will produce a shrinkage of an enlarged prostate, although the end-results will vary with each patient. As the operation of prostatectomy has been recently perfected and the mortality greatly reduced, the use of the X-ray in reducing enlargements of the prostate is naturally relegated to those cases in which operation is contra-indicated or refused. In the latter type of cases, however, deep X-ray therapy supplies the only satisfactory means of relieving the symptoms.

The treatment should be administered by cross-firing at the prostate through multiple portals of entry, preferably four anteriorly, four posteriorly and two on the perineum.

559. Line 23 to 560. Line 44 (inclusive) (B. F.). 555. Line 23 to 556. Line 44 (F.) *substitute*:

By the use of the Coolidge tube the production of atrophic changes in the human ovary is one of the safest and surest therapeutic procedures. The treatment may be so regulated as to merely inhibit ovarian activity or to abolish the ovarian function entirely. These effects may be brought about in any menstruating female irrespective of age. The amount of X-ray exposure required varies with the age of the patient, decreasing as the patient approaches the age of natural menopause. The permanency of the induced menopause likewise varies with the age of the patient. In patients from thirty-five to fifty the cessation of menstruation is usually permanent. In patients under thirty years the menstrual function will probably be reëstablished after a lapse of two to three years.

The artificial menopause thus induced is, as a rule, not accompanied by any unpleasant symptoms. A considerable percentage of cases will experience the characteristic hot flushes.

The X-ray method finds clinical application in menorrhagia, uterine fibroids and dysmenorrhea. In either of these conditions the favorable results are brought about through inhibition or abolition of ovarian function, although it is generally conceded that the X-ray has a direct influence upon the uterine fibroids, causing a slow fibrosis and shrinkage of the tumor masses.

The selection of cases is of paramount importance for obvious reasons. Every effort should be made to exclude malignancy. Furthermore, a most rigorous examination should be made to exclude inflammatory or other pelvic lesions which may demand surgery. The difficulty in the selection of cases is the chief criticism of this method of therapy, and the improper selection of cases is the usual cause of the failures.

This method should not conflict with surgery, but finds its chief application where surgery is not indicated or refused. As a method of last resort, it is often of life-saving value.

Depending upon the urgency of the symptoms, the artificial menopause may be given and the results may be awaited after several months' time.

The treatment is administered by the cross-fire method through multiple portals of entry. The irradiation is given both through the abdomen and through the back. The following simple technic may be advantageously employed: Four portals of entry should be used, two anteriorly and two posteriorly. Rather large areas should be blocked (about three inches square) so that the divergence of the rays will be sufficient to include both ovaries at each dose. A Coolidge tube backing up a nine to nine and one-half parallel spark gap should be employed. The rays should be filtered through three millimeters of aluminum and a thick piece of leather. The target skin distance should be eight inches. A dosage of fifteen X to twenty X should be given over each area once a

week. The total dosage will vary from 100 X to 800 X, depending upon the age of the patient. If the patient is approaching the natural menopause one series of exposures (100 X) may be sufficient. The treatment may be pushed until a period is missed or the estimated required dosage may be given and the results may be awaited after several months' time. The cessation of menstruation may be abrupt or there may be a gradual diminution in the successive menstrual flows. Temporary increase of the menorrhagia or metrorrhagia during time occupied by the treatments or shortly thereafter occurs occasionally, but this is without significance and does not influence the final results.

CHAPTER XIII

NUTRITION AND DIETETICS

WARREN COLEMAN

603. Lines 7-10 (B. F.). **559.** Lines 7-10 (F.) *read*:

Dietetics, on the other hand, relates to the selection of foods, **the arrangement of dietaries which cover the nutritive requirements and, at the same time, conform to** the likes, dislikes, and idiosyncrasies of persons, and the methods of preparing and serving the food.

Line 27 (B. F.). **559.** Line 27 (F.) *add* after "labor.":

It should be added that the vitamines content of the food must be unimpaired.

604. Lines 6-11 (B. F.). **600.** Lines 6-11 (F.) *read*:

Foodstuffs are classified as follows:

Proteins,
Carbohydrates,
Fats,
Vitamines,
Inorganic substances,
Water.

Line 22 (B. F.). **600.** Line 22 (F.) *add* after "cogen.":

Vitamines.—These are complex organic substances occurring in small quantities in many foods, upon which health and life itself depend.

605. Lines 11-12 (B. F.). **601.** Lines 11-12 (F.) *read*:

Gelatin.—Gelatin **and some other proteins, e.g., zein,** cannot supply material for the building and repair of the body, but Murlin has shown that **gelatin** may

607. Line 8 (B. F.). **603.** Line 8 (F.) *add* after "metabolism.":

THE VITAMINES

It has long been known that scurvy develops in persons confined to diets of preserved meats, dried vegetables, and hardtack, and that the

disease is cured by fresh foods, especially fresh vegetables and lime or lemon juice. Children develop infantile scurvy when their diet consists solely of boiled or pasteurized milk. One of the older theories regarding the etiology of beriberi attributed the disease to polished rice, that is, rice from which the pericarp and germ have been removed.

The development of these diseases in no way depends upon deficiency in the protein or energy content of the food. For a time it was thought that scurvy was due to a lack of special salts or changes in the salts brought about by the preparation or preservation of food. But, gradually, it became evident that foods contain substances which are not the ordinary foodstuffs or salts upon which the maintenance of health or life depends. Experimentation has established this beyond dispute.

Funk suggested the term *vitamines* for these substances on the ground that they are essential to life and that they are related chemically to the amines. He states that they are very complex, nitrogen-holding, crystalline bodies, belonging to a new chemical group. Their exact chemical nature has not yet been worked out. The vitamine from rice polishings is believed by some investigators to be a pyrimidin base.

Foods contain vitamins in very small quantities; in rice polishings the proportion is 1 to 100,000 parts. Vitamins are easily destroyed by heat (except that the vitamine in lime juice may be boiled for an hour without injury) and by keeping foods (after several months). Though a number of vitamins are known to exist, they have been isolated only from rice polishings and yeast.

Vitamins are present in meat, eggs, milk, cereals, all rapidly growing vegetables, and fruits, especially limes, lemons, oranges, and apples. Some foods, for example milk, contain more than one vitamine.

The manner in which the vitamins act to prevent disease and preserve life is unknown. It has been suggested that they play the rôle of activators or hormones. The onset of beriberi is hastened by diets which contain an abundance of carbohydrate, which suggests that the beriberi vitamine controls in some unknown way the metabolism of this foodstuff.

The relation of the vitamins to nutrition and disease is of the highest importance. Vitamins are necessary for the normal growth of animals. In their experiments on rats, Osborne and Mendel proved the existence of a growth vitamine in milk. Hill and Flack found that a growth vitamine is present in whole-wheat flour, but not in white flour, owing to the removal of the outer layers of the grain and the germ. The bearing of such facts upon the nutrition of the people, particularly the children of the poor, is self-evident.

The lack of vitamins is responsible for at least two diseases, namely, beriberi and scurvy (for etiological relationships the reader is referred to the chapters on these diseases). Pellagra is attributed by some to a similar deficiency. Funk suggests that sprue, tropical endemic

neuritis, spasmophilia in children, and osteomalacia may have a like origin.

Another phase of the vitamine problem relates to commercial foods recommended for children and invalids. The instability of the vitamins makes it improbable that many, if any, of them contain vitamins. If circumstances compel the employment of such foods, the vitamine supply should be insured by the addition of suitable articles to the diet. Hess succeeded in preventing scurvy in children fed on pasteurized milk by giving orange juice.

608. Line 33 (B. F.). 604. Line 33 (F.) *add* after table:

The total energy requirement may be expressed as calories per kilogram per day or calories per square meter of body surface per hour. The latter method is the more accurate, and the chart recently published by DuBois and DuBois makes the method practicable for bedside work (see Chart).

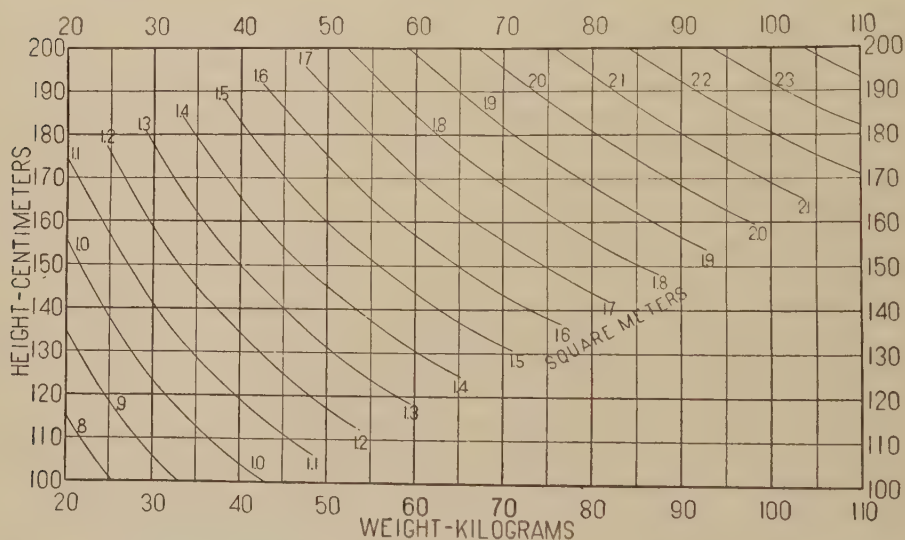


FIG. 1.—CHART FOR DETERMINING SURFACE AREA OF MAN IN SQUARE METERS FROM WEIGHT IN KILOGRAMS AND HEIGHT IN CENTIMETERS. The point of intersection of ordinate and abscissa for any individual is found and the surface area read off on the curved lines. For example, if a man is 150 centimeters in height, and weighs 60 kilograms, his approximate surface area will be 1.55 square meters. (After DuBois and DuBois.)

Lines 35-37 (B. F.) 604. Lines 35-37 (F.) *read*:

without voluntary movement of any kind) and **twelve hours or so after** food is 22-26 calories per kilogram per day, or 1,540 to 1,820 calories for a man weighing 70 kilograms (154 lbs.). **The total energy requirement by surface area is 39.7 calories per square meter per hour.** Patients confined to bed are never at absolute

609. Lines 8-18 (B. F.). 605. Lines 8-18 (F.) *read:*

Age.—The rate of metabolism varies with the age of the individual. It is greatest in infancy and childhood and lowest in old age. As will be seen on the chart (Fig. 2), metabolism, which is low at birth, rises rapidly during the first year and reaches its maximum somewhere between the first and sixth years (this period has not been thoroughly investigated). After the sixth year it falls rapidly until the age of twenty and thereafter very slowly. There is no difference between the sexes in infancy. After the sixth year girls and women have a distinctly lower metabolism. DuBois found the heat production of boys, 12 to 13 years old, to be 25 per cent. above the adult level. A surplus over the actual demand

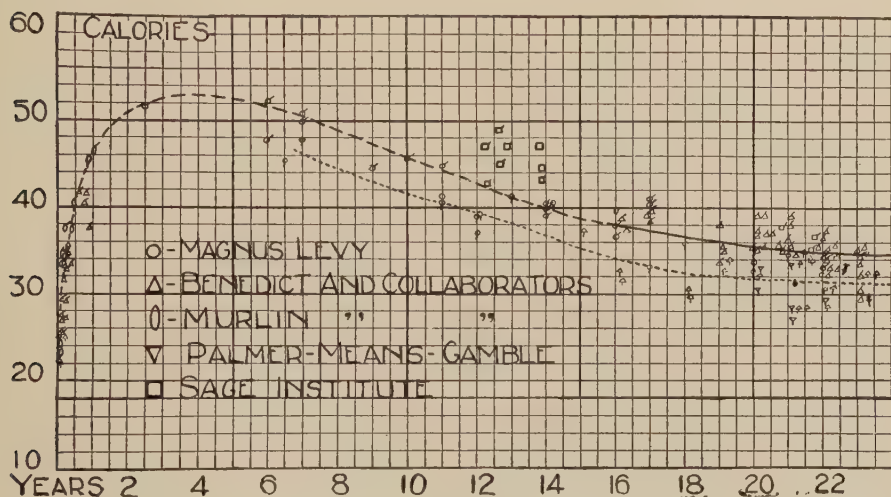


FIG. 2.—CHART SHOWING VARIATIONS OF BASAL METABOLISM WITH AGE: CALORIES PER HOUR PER SQUARE METER OF BODY SURFACE—MECH'S FORMULA. Dash line shows average for males, dotted line for females. (After DuBois.)

649 (B. F.). 645 (F.). *Add* after tables:

METABOLISM IN FEVER

The Total Metabolism.—The loss of weight, which until recently has always accompanied prolonged high fever, early led to the belief that the intensity of the metabolic processes in fever is increased. This belief remained unchallenged for many years, in fact, until attempts were made to calculate the heat production of patients with fever from measurements of the respiratory exchanges.

The increase of the nitrogen excretion in the urine has generally been accepted as indicating a more rapid destruction of protein. The

discussions have centered around the total heat production and the extent to which carbohydrate and fat participated in the metabolic processes.

A rise of the body temperature may be brought about by an increase in heat production without change in heat elimination, by a decrease in heat elimination, the heat production remaining unchanged, or by other disproportional alterations of heat production and heat elimination. In probably no disease does the heat production reach such levels as normally occur during violent and prolonged muscular exertion, yet the body temperature is not affected by it. In exophthalmic goiter the metabolism may be 75 per cent. above normal without producing fever. Therefore, it is evident that increase in heat production alone is not sufficient to cause fever. The heat regulating mechanism must be altered. It is "set" in fever for a higher level of body temperature just as a thermostat is set for a higher temperature in an incubator.

Quantitative Changes.—The total heat production of the body may be learned by direct measurement of the heat given off (direct calorimetry) or be calculated from the respiratory exchanges and the nitrogen of the urine (indirect calorimetry). DuBois has shown with the aid of the calorimeter of the Russell Sage Institute of Pathology that the two methods agree within 2.2 per cent.

The earliest studies of the total heat production in fever by indirect calorimetry gave inconstant results. In the majority of cases an increase was noted, but other cases were observed in which it was normal or even decreased. As a result of these differences the theory was advanced that fever might occur without increase in heat production, that is, from decrease in heat elimination. But the results obtained in the investigations of Coleman and DuBois and the fact that many of the earlier observations have been proved unreliable, incline the author to the belief that fever is always accompanied by increased heat production. There has always been an increase during the febrile period of typhoid. The total metabolism was roughly parallel to the temperature curve, though there were considerable variations in different patients and in the same patient at different stages of the disease. The average increase amounted to 40 per cent., the maximum to something over 50 per cent.

Without entering into the discussion of the significance of fever in the infective diseases, some of the factors to which the increase in heat production has been attributed require consideration.

An early explanation ascribed the increase to the greater destruction of protein. This theory has been abandoned except in so far as the protein metabolism contributes to the general increase.

Fr. Mueller suggested that the increase in metabolism might be due in part to the increased rapidity of the heart and respiration and to muscular effort—restlessness, rigors. The most recent studies indicate

- that the amount of energy liberated by the heart and muscles of respira-

tion is insignificant when compared to the total; at least, it plays no considerable part in increasing heat production in fever. In typhoid the pulse is characteristically slow. But few observations have been made on the amount of energy required to perform muscular work in fever. Svenson found in convalescence from typhoid that muscular work is not done economically. It may not be done economically during the febrile period, yet according to evidence which we possess the increase in total metabolism is greater than could be accounted for by restlessness. A patient was unusually quiet during the first hour of a three-hour period in the calorimeter; during the second hour he was restless and tossed about the bed; during the third hour he was restless and irrational. Yet during the whole period his metabolism was only 43 per cent. above normal, and was only 5 per cent. higher than it was during a quiet observation made two days later when the temperature was lower. In the typhoid state, when the patient is rarely quiet, the increase in heat production from muscular effort must be great—it is conceivably doubled. In the ordinary case of typhoid the amount of the increase from moving about the bed has been *estimated* to be about 10 per cent.

The influence of food upon the total metabolism during the febrile period is negligible. The increase from protein is 5 per cent., from carbohydrate 1 per cent. In convalescence food has caused an increase of 16 per cent. in heat production, but without affecting the body temperature.

Qualitative Changes.—When the nitrogen of the urine is known, the amounts of protein, carbohydrate, and fat consumed during stated periods may be calculated from the O_2 consumption and the respiratory quotient. The respiratory quotient, or coefficient, is the result obtained by dividing the CO_2 output by the O_2 consumed.

By reason of its chemical composition, when carbohydrate is oxidized to carbon dioxid and water the amounts of CO_2 liberated and O_2 consumed are equal and the respiratory quotient is 1.0. When fat is oxidized to the same end-products the respiratory quotient is 0.7. When protein is oxidized to urea the quotient is 0.8. When the body transforms carbohydrate to fat the quotient is over 1.0, because fat is poorer in oxygen than is carbohydrate. Since under actual conditions some protein is constantly metabolized, the respiratory quotient may vary from something over 0.7 to somewhat under 1.0. When the body is storing fat the quotient is slightly under, or over, 1.0.

The respiratory exchanges of fever patients have been studied both during the fasting state and after food. The data which have been accumulated permit a reasonably clear conception of metabolic processes in fever to be formulated.

The low respiratory quotients, that is, under 0.7, which have been obtained by some observers, and which can only be interpreted by assum-

ing that profound changes occur in the metabolic processes in fever, are now attributed to errors in technic.

As will be seen later, the nitrogen metabolism probably is increased. But no qualitative change in the nitrogen metabolism has been observed. Protein is oxidized to the same end-products as in health—urea principally—and liberates the standard amount of heat per unit of substance. No qualitative changes are known in the metabolism of carbohydrate and fat. Both are oxidized to carbon dioxid and water and, similarly, produce the calculated amounts of heat. The law of the conservation of energy obtains in fever as well as in health.

The respiratory quotients prove that carbohydrate and fat are metabolized under the same general laws as in health—only the rate of utilization is changed. When available, carbohydrate is consumed in preference to, and in greater quantity than, fat, just as in health when an increased demand for energy has to be met. When carbohydrate is not available, fat (of the food or body stores) is utilized. It is still doubtful whether fat is as capable of protecting body protein as is carbohydrate. In a mixed diet they appear to be equally good as protein-sparers, within limits which have not yet been determined. The carbohydrate supply is more rapidly exhausted in fever than in health, whether in the form of the unchanged carbohydrate of the blood or the glycogen of the tissues, and should be frequently replenished.

The Nitrogen Metabolism.—On low diets the nitrogen metabolism is always increased in the infective fevers. More nitrogen leaves the body in the urine than is taken in with the food. Consequently, the store of nitrogen is constantly depleted; the patient is said to be in negative nitrogen balance. In severe forms of the infective fevers, such as pneumonia and typhoid, the losses, relatively speaking, may be very great. In general, the extent of the loss is proportional to the severity of the infection. It is always greater than in simple starvation.

This loss of nitrogen in the infective fevers has been known for many years and has been called the *febrile or toxic destruction of protein*. Accordingly, it has been considered a characteristic phenomenon of infective fevers.

Several conceptions of the nature of the process are found in the extensive literature on the subject. Von Leyden and Klemperer describe it as a loss of nitrogen which cannot be prevented by food. According to Benedict and Suranyi, it is merely an expression of the increase in total metabolism. Krehl and Fr. Mueller use the term to indicate direct injury to the cells of the body by the toxin of the infecting organism. These different conceptions have led to much confusion in discussions of the subject. It should be stated here that Grafe and his pupil, Rolland, deny the existence of a toxic destruction of protein in fever.

By their success in bringing patients with severe attacks of typhoid

fever into nitrogen equilibrium, Shaffer and Coleman showed that the conception of von Leyden and Klemperer is no longer tenable.

The main objection to the theory of Benedict and Suranyi lies in the fact that the nitrogen metabolism of normal men does not rise with the increase in total metabolism which occurs during muscular effort. Moreover, the increase in nitrogen metabolism appears to be greater than can be explained by the increase in total metabolism in fever.

Krehl's theory of the toxic destruction of protein is at present the center of active discussion. The opponents of the theory, when not denying its occurrence, maintain that the increase in nitrogen metabolism is due to the rise in the body temperature rather than to an injurious action of toxins on the cells.

1. *The Influence of High Temperature.*—A large number of experiments have been performed on lower animals and man in the attempt to discover the extent to which nitrogen metabolism is influenced by high temperature. The body temperature has been raised artificially by puncture of the heat center, by hot-air, hot-water, and steam baths, and the nitrogen output determined. The nitrogen output of patients with various types and heights of temperature curves has been studied during the febrile and afebrile periods.

The results of these experiments have not been uniform. Senator and Richter explain negative results by saying that increase in the metabolism of protein occurs only when the high temperature is maintained for a number of hours, and that the increase of nitrogen in the urine may not at once be apparent. Graham and Poulton, experimenting upon themselves, did not succeed in increasing the nitrogen output by raising the body temperature by steam baths.

The observations in various febrile diseases and on experimentally infected animals have been equally inconstant. In some instances the nitrogen excretion has paralleled the temperature curve; in some it has been high when the temperature has been low, and an increase in the nitrogen excretion has been observed before the rise in temperature occurred. Linser and Schmid state that the nitrogen excretion is affected only by temperatures of 39° C. and over.

2. *The Influence of the Toxins.*—The discrepancies in the relation of the nitrogen excretion to the body temperature led to a search for other causes. Krehl attributes the increase in nitrogen metabolism to a deleterious action of the toxin of the invading organism on the cells of the body.

Commenting on May's experiments on animals, Fr. Mueller says the fact that carbohydrate diminishes the protein loss in fever would not disprove the theory of a toxic destruction until it had been shown that like amounts of carbohydrate reduce the nitrogen exchanges of men with high fever to as low a level as in health. Shaffer and Coleman have shown that this is impossible in typhoid fever. Their patients could not

be brought into nitrogen equilibrium until they were given amounts of food representing an energy value of 50 per cent. to 100 per cent. above their heat production (computed from measurements made later with the Benedict "universal" apparatus and the Sage calorimeter). It was also found that the nitrogen intake could not be reduced much below 10 gm. without throwing the patient out of nitrogen balance. Rolland's patients with sepsis, paratyphoid, and acute pulmonary tuberculosis had a nitrogen metabolism not greater than the lowest requirements in health. She brought them into balance on amounts of protein slightly greater, or within the figures given by Rumpf and Schumm (1.15 gm. per kilogram) and by Chittenden (0.7 gm. per kilogram), but with an excess of carbohydrate. She did not take the nitrogen minimum into consideration, that is, the smallest amount of nitrogen to which a healthy man can be reduced for short periods, together with sufficient amounts of carbohydrate and fat to cover his energy requirement, without developing a negative nitrogen balance.

Recently Kocher, working under Fr. Mueller's direction, has made a further study of the subject. He compared the effect of an increase in the total metabolism (through strenuous exercise) of two healthy individuals upon their nitrogen minima with the nitrogen excretion of fever patients on diets containing essentially the same quantities of protein and amounts of energy, which, *he calculated*, were sufficient to bring them into nitrogen equilibrium. Since the fever patients lost nitrogen, while the healthy men did not, he concluded that the occurrence of a toxic destruction had been established. Kocher's experiments are open to the objection that he did not first bring his patients into equilibrium and then reduce the protein, as Shaffer and Coleman did. Grafe has published experiments on animals which, he claims, disprove Kocher's conclusion.

The author believes that the protein metabolism is increased in the infective fevers. The fact that typhoid patients cannot be brought into nitrogen equilibrium unless they receive from 10 to 15 gm. of nitrogen a day, and an amount of energy from 50 per cent. to 110 per cent. greater than their heat production, can, in his opinion, be interpreted in no other way. But whether the increase in protein metabolism is due to the elevation in temperature or to injury from the toxins is, likewise in his opinion, an open question.

The most important consideration for the practitioner is that it is possible to nourish fever patients in a manner which prevents loss of nitrogen to the body.

The Absorption of Food in Fever.—Von Hoesslin found in 1882 that food is absorbed by typhoid patients almost as well as in health, in spite of the fact that most of his patients suffered from diarrhea. About the same time (1883) similar observations were made in Chud-

nowsky's clinic in Russia. Von Leyden and Klemperer's patients with high fever lost in the stools 6 per cent. to 11 per cent. of fat and 9 per cent. of protein. No carbohydrate was lost except when large amounts were given or the patients had profuse diarrhea. Recently DuBois has reinvestigated the question of food absorption in typhoid fever, using more reliable methods of analysis. He found the losses to be as follows: There was no loss of carbohydrate except when the patients were taking more than 300 gm. a day; then it amounted to only 2 or 3 gm.; the average loss of protein was 7 per cent.; the average loss of fat for all stages of the disease was 6 per cent. (the loss of normal controls on the same diet was 3 per cent.); for the early stages the loss was 7 per cent., for the later 4.5 per cent. It should be added that the patients were taking large amounts of fat. In Coleman and Gephart's typhoid patients the average fat loss in all periods of the disease was 4.3 per cent. No differences were observed between the early and later stages. The nitrogen losses averaged 11 per cent.

These observations prove that in typhoid fever, and probably in other febrile diseases, the absorption of food is nearly as complete as in health.

THE FEVER DIET

The facts which have been obtained through studies of metabolism in fever have removed all doubt that patients with fever require more food than healthy men, unless engaged in heavy labor. The only question is whether fever patients can take the amount of food they need without detriment. The answer is to be found in clinical tests, without which it is impossible to estimate the value of any therapeutic procedure. These tests have been made on a large scale, and the results prove not only that fever patients can take without harm the amount of food they need, but that they are benefited by doing so.

Diets which do not furnish enough energy to cover the patients' heat production compel them to live in part at the expense of their own tissues. Experiments with such diets extend back some 2,000 years in medical history, and the results, to say the least, have been disappointing.

The food needs of the fever patient may be summarized as follows:

The total energy required is always greater than in health. In general, the higher the temperature, the greater the need for food. In typhoid fever the body protein is not protected unless the food furnishes from 50 to 110 per cent. more energy than the heat production. This is probably true for many infective fevers. There is some disagreement whether patients should be given such large amounts of food, but patients digest them well, and the author can see no justification for permitting a gratuitous loss of protein. Expressed as energy, patients with severe fever require from 3,000 to 4,000 calories a day. If they complain of hunger,

as typhoid patients frequently have while taking this amount, the food may be increased. The author has permitted as much as 7,600 calories.

The amount of protein which the patient needs varies from 60 gm. to 90 gm. Patients lose nitrogen if less than 60 gm. be given, and they derive no benefit from more than 90 gm.

Carbohydrate is consumed in preference to fat, whenever it is available, and should be the main reliance for maintaining the energy value of the diet. When the desired amount of carbohydrate is not easily digested, the quantity of fat may be gradually increased. The arrangement of dietaries will be simpler if fat is included (butter and cream), and with some patients it must be depended upon to supply the greater portion of the energy. As much as 300 gm. of fat a day has been given.

One of the most important considerations in the dieting of fever patients is *individualization*. Every effort should be made to "feed the fever," but this can be accomplished only if the patient digests and absorbs the food he receives. With so many foods from which to choose, it will rarely be necessary to insist upon a patient's taking foods he dislikes. His desires should be followed as far as is feasible both in the selection and preparation of his food. Foods which disagree should be avoided. Torrey has shown that the inability of the typhoid patient to digest his food is associated with a predominance of a putrefactive flora in the intestine. The equally important fact, disclosed by his investigation, was that favorable fermentative types of organisms usually gain the ascendancy on diets rich in carbohydrate.

Much greater variety in food may be allowed than was formerly thought permissible. The author has practically abandoned the use of the milk diet except for brief periods and under unusual circumstances. Milk is a valuable addition to many dietaries, but, alone, it furnishes too much protein and too little energy. If a carbohydrate is taken with it, such as bread, crackers, simple cake, it is not only more easily digested but patients enjoy it more. Milk may serve also as a vehicle for other foods—milk sugar, eggs, and cream.

The food should be served as far as possible in the form and manner most likely to stimulate the patient's desire for it. Small quantities at frequent intervals—but not oftener than every two hours—are digested more easily than fewer, but larger, meals. In severe fevers the patient should be waked for his food, except perhaps during the early morning hours. The appetite may be stimulated and flow of gastric juice started by beginning the larger meals with two to four ounces of meat soup. This amount will not compromise stomach room.

The foods which the author has found most useful are: Milk, cream, eggs, bread or toast, crackers, well-boiled and bran-free cereals, rice, well-cooked potato, butter, bacon (as a relish), milk sugar, cane sugar, tea

and coffee (as vehicles and for variety), cocoa, apple sauce, orange juice, lemonade, and grape juice.

Any digestible combination of these foods may be given (*see* The Invalids' Dietary).

The more easily digested meats may be permitted in small quantities once a day, preferably at mid-day. Foods containing cellulose may be allowed to patients whose alimentary tracts are not the seat of pathological processes.

657. Lines 8-9 (B. F.). **653.** Lines 8-9 (F.) *read*:

causing disturbances of digestion. Another, and **more** important, fact is that the **deficiency of vitamins** in proprietary foods has

665 (B. F.). **661** (F.). *Add* under "References.":

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Chudnowsky. *See* Atwater and Langworthy, *Digest of Metabolism Experiments*, U. S. Dept. Agric., Bull. No. 45, 1897, p. 181.

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———. *Ibid.*, 1916, XVII, 887.

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VOLUME II

I. INFECTIOUS DISEASES

CHAPTER I

TYPHOID FEVER

FREDERICK C. SHATTUCK

4. Line 20-21 *read*:
men involved is larger for the Maneuver Division. The following is a **summary** referring to the former, from the celebrated "Report on Typhoid."

Substitute for tables:

In the regiments of the Second Division of the Seventh Army Corps assembled at Jacksonville, Fla., in 1898, in which the mean strength amounted to 10,759 men, there were 1,729 certain cases, and 2,693 classified as certain and probable cases of typhoid fever. There were 248 deaths from typhoid fever and 281 deaths from all diseases.

In the organizations composing the Maneuver Division at San Antonio, Texas, from March 10th to July 10th, 1911, in which there was a total mean strength of 12,659 men for the month of June—there was but one case of typhoid fever, no deaths as a result of typhoid fever, and eleven deaths from all diseases. In addition, a civilian teamster, not immunized, was admitted for typhoid fever in April. "The case, a private of the Hospital Corps, had not completed his immunization, having taken only two doses. The case was very mild and would perhaps have been overlooked but for the rule that blood cultures were made in all cases of fever of over 48 hours' duration. The Widal reaction has no diagnostic value in immunized persons, as all respond to it. Forty-nine cases of typhoid fever with nineteen deaths were reported as occurring in the city of San Antonio during this period."

6. Line 44 *add* as footnote after "Hospital"¹:

¹ For full and minute details as to the use of vaccines and sera the reader is referred to the special article on these agents in Vol. V.

Here it suffices to state that the enormous value of antityphoid vaccination has been fully borne out in the present war. Dr. David Chevon tells me that there was not a case of typhoid in the base hospital of the British Expeditionary Force under the Harvard Unit, which he headed for three months. The absence of typhoid under trench life and other conditions of the war now raging seems conclusive evidence that the freedom of our own little army cannot be due simply to the enforcement of better sanitary methods, as has been claimed by some.

Even if the immunity conferred by vaccination is not absolute, as is suggested by the rare occurrence of the disease within a few months after protection, its relative value would seem to be beyond question. The protection afforded by vaccination against smallpox is less complete and lasting in some than in most people. Why may it not be the same here? We do not consider the above fact a sufficient warrant for impugning smallpox vaccination.

Typhoid and the paratyphoids, however closely allied, are not the same. The paratyphoids are less alike in mortality and morbidity. In troops at least, especially if about to engage in active service, it is better to protect against both. Whether the respective vaccine should be given separately or combined seems still an open question. If a sufficient dosage of each cannot be given in combination it would seem clear that the vaccines should be given separately.

Whether two injections are as protective as three, we do not know.

In view of the good results obtained by them, of the trifling economy of time and trouble secured by the omission of one injection, and of the fact that we have no such ready and sure criterion of a "take" as we have in the case of smallpox vaccination, the reduction would seem to involve taking chances unwarrantable in the present state of knowledge.

CHAPTER II

TYPHUS FEVER

ALVAN H. DOTY

Typhus fever is an acute infectious disease, abruptly ushered in and associated with a general eruption and an early and profound involvement of the nervous system. It more markedly ends by crisis than any other disease—usually from the twelfth to the fourteenth day.

There are three diseases which in the past have been responsible for great loss of life. These are plague, cholera and typhus fever.

Nothing more clearly reflects the value of modern sanitation than the control or extermination of these diseases. This relates particularly to typhus fever, which has so long been identified with overcrowding, filth and poverty that it is commonly known as "prison fever," "ship fever" and "famine fever," indicating the favorable conditions for its appearance and dissemination. Until its activity during the present European war, typhus fever had reached a remarkably quiescent state and except in Mexico it had practically disappeared from this continent.

Abundant and conclusive proof has been presented as to the connection of this disease with filth, overcrowding and an impoverished condition of the people whom it affects.

It is fair to assume that, with the knowledge we now possess concerning the source of infection in typhus fever, and the known preventive measures which may be employed, as well as the improved methods of prevention at foreign ports of departure, relating to observation, medical inspection and detention of those about to embark, this disease should in the future be far less of a menace to the public than it has been in the past, and its extermination may be hoped for.

Source of Infection.—It was formerly believed that typhus fever, like various other infectious diseases, was transmitted through the medium of fomites. This applies to such articles as clothing, baggage, money, and the like, which were believed to convey infectious organisms in their active state from one person to another. This theory, although erroneous,

has been handed down for generations, and until recent years has been generally accepted as the common means of infection in typhus fever.

Nicolle, in France in 1909, was the first to report that typhus fever is transmitted from one person to another by the body louse (*Pediculus vestimenti*). His statement was subsequently confirmed by the researches of Ricketts and Wilder of the University of Chicago, and afterwards by Anderson and Goldberger of the U. S. Public Health and Marine Hospital Service, whose investigation was carried out in Mexico. This belief is in harmony with certain peculiarities of infection which are familiar to those who have dealt with typhus fever, for it is notoriously confined to persons of the class who would naturally be the hosts of these insects. For instance, during the outbreak of typhus fever in New York in 1892 and 1893, of the large number of cases dealt with by the Department of Health, only two or three of the number were from the better walks of life. In all other cases those who contracted the disease formed part of the tenement and lodging population of the city.

Etiology.—Various protozoa and bacteria have in the past been considered as possible causes of typhus fever, but none of these has shown final tests with the probable exception of the last which was cultivated by Plotz in the laboratories at the Mt. Sinai Hospital. This organism is a nonmotile, small and generally Gram-positive pleomorphic bacillus. Its length is from 0.9 to 1.9 microns and its average breadth two-fifths as great. It is not acid-fast, does not produce spores and produces no visible capsules. It does not pass through the Berkefeld filter.

The bacilli are strictly anaërobic and are first cultured by adding the blood of the patient to melted glucose serum agar, contained in long test tubes. The colonies are usually numerous in cultures made from blood taken during the first days of the disease, and generally negative from blood taken at the crisis and uniformly negative from blood obtained from more than 36 hours after the crisis.

The blood taken early in severe cases may yield several hundred colonies from each c.c., but as a rule only a very few develop, and in about fifty per cent. of mild endemic cases no culture develops. Only a highly trained bacteriologist with exact knowledge of the technique can hope to obtain a culture. Up to the present time no others except those trained by the Mt. Sinai workers have been successful.

Successful results have also been obtained from the blood of infected guinea pigs and monkeys.

Olitsky has made extensive studies on the immune bodies in convalescent cases and found that complement fixing antibodies and agglutinins developed rarely before the crisis, but most extensively between the third and tenth day after. The antibodies, after reaching the maximum, were found to diminish gradually.

Persons who have been in close contact, but who have not had any

symptoms, sometimes develop antibodies. Those who have not had this disease so far as they know and have not knowingly been in contact with cases have antibodies very rarely.

The cultures in the glucose serum media lose their virulence almost immediately, and these cultures do not have the property of immunizing susceptible guinea pigs and monkeys. This is peculiar, as the animals have immunity when they have recovered from the disease. The use of the vaccine must, therefore, be understood as still in the experimental stage, and there is no proof yet of its being of value. The reports of its use in Mexico thus far are not encouraging. The European results appear to be favorable but have not been fully reported. Our present information points very strongly to the bacillus isolated by Plotz being the causative microörganism, but until cultures are obtained which keep their virulence or have the power to immunize human beings or suitable animals a doubt will remain. It is hoped that the investigations which are being carried on in Europe will determine conclusively the nature of this bacillus.

[Sellards (Sellards, A. W., Jour. Immunol., 1916, I, 321) reports the isolation from spleens removed from patients suffering from pernicious anemia, of an anaërobic bacillus which resembles very closely in its cultural and immunological reactions the bacillus isolated from typhus fever by Plotz, and suggests that the two organisms are closely related and may be parasitic but nonpathogenic in the human body.—EDITORS.]

Incubation and Invasion.—The incubation of typhus fever usually covers a period of from eight to twelve days.

The invasion is abrupt and very brief, and in this respect is particularly characteristic of this disease. A person may retire apparently in good health and be seized during the night or in the morning with a headache and a chill or a chilly sensation. Headache is practically always present. The face becomes flushed and the conjunctivae are congested. These are early and constant signs of typhus fever. To this may be added an early involvement of the mental faculties. It is the latter which has given the name of typhus to this disease, the word typhus indicating stupor and relating to the confused condition of the mind.

Temperature.—The temperature curve is very characteristic, and is best understood by a study of the accompanying charts, which are typical and indicate the range of temperature in actual cases which occurred during the epidemic of typhus fever in New York City in 1892-1893.

The temperature rises rapidly and usually attains its height at 104° or more, about the fourth or fifth day of the disease, when it becomes stationary, with some diminution in the morning. After the ninth or tenth day, in favorable cases, the temperature begins to decline, and usually continues so until recovery. From the twelfth to the fourteenth day the temperature as a rule abruptly drops to normal or subnormal;

this is particularly characteristic of the disease, for typhus usually terminates by crisis at this time.

The Eruption.—On the second to the fourth day of typhus fever the characteristic eruption appears; the diagnosis of no other disease depends more fully upon this sign. Without it a diagnosis cannot consistently be made.

While there are other forms of infection which may produce an eruption somewhat similar to typhus fever, that of the latter disease may as a rule be confirmed if sufficient time is given for this purpose. The eruption of typhus fever is quite apt to be present when the physician first sees the patient.

The true or diagnostic eruption of typhus fever is petechial, due to

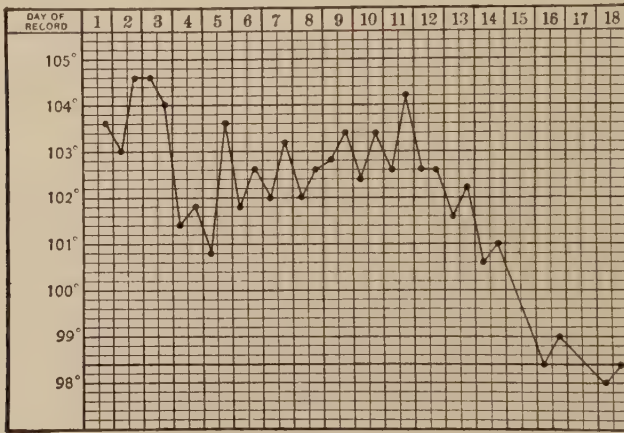


FIG. 1.—CASE OF TYPHUS WITH GRADUAL DECLINE OF TEMPERATURE, FOLLOWED BY RECOVERY.

a minute hemorrhage in the center of the spot. It can be easily understood that such a condition would occur in the presence of great prostration and weakness of the vascular system. The eruption is general over the body, and may be particularly well studied on the flexor surface of the forearm or about the shoulders. The eruption does not occur in successive crops as in typhoid fever, but as one crop, although it may be irregular in arriving at its completion. It may last eight or ten days, and is usually present when death occurs, prior to the end of the second week. In some cases a slight desquamation may follow. However, this is of no diagnostic importance.

A more minute description of the eruption is as follows: At first it does not assume its true character, but appears as a rash which sometimes may be mistaken for measles. The spots are irregular and vary in size from a pea to those which are much smaller. They may be isolated or rather grouped in patches, and do not at first present the characteristic

dark rose-colored appearance, and may even disappear on pressure. The eruption generally presents itself first on the chest and abdomen, and afterwards on the arms and thighs. On the face and neck it is not only pronounced but frequently may not be detected. This has been ascribed to the very vascular condition of this part of the body, added to the extreme hyperemia which occurs in typhus fever. There is some reason to believe that this is the proper explanation. In addition to the eruption above referred to, a mottling of the skin may occur.

The early eruption soon undergoes a change. The spots become darker in color, and do not disappear on pressure. Subsequently there

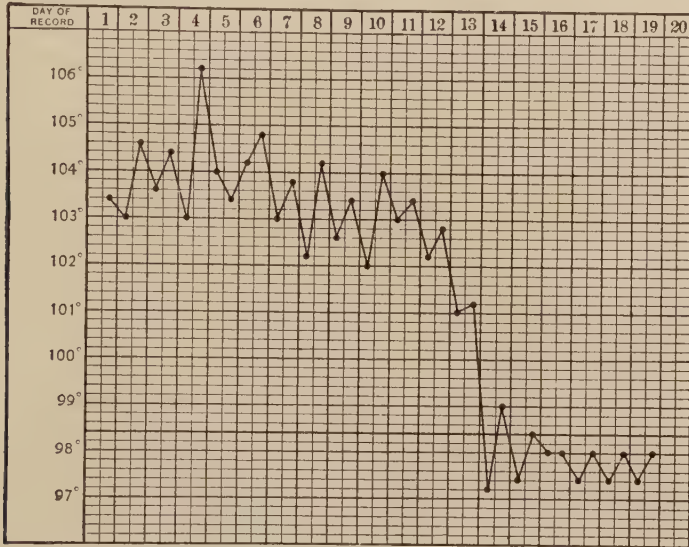


FIG. 2.—CASE OF TYPHUS WITH DECLINE OF TEMPERATURE BY CRISIS, FOLLOWED BY RECOVERY.

appear in the centers of the spots dark bluish points known as petechiae, due to minute extravasations of blood. This practically represents the true eruption of typhus. To complete the picture, a dusky or congested appearance of the surface of the body is present, whereas in typhoid fever, for instance, the skin retains its normal color, or is even paler.

Prognosis.—Age has largely to do with the prognosis. Very young children do not often die from it, and those who succumb are usually beyond early youth; after this the mortality increases, and at the age of fifty the mortality is generally from forty to fifty per cent., particularly among those who are addicted to the excessive use of alcohol or have organic diseases or other debilitating causes. One attack of typhus fever generally confers immunity.

There is one factor present in typhus fever which is probably more constant than in any other disease, i.e., the termination by crisis about

the fourteenth day. It is very important that this should be borne in mind, particularly in doubtful cases; furthermore, the prognosis of typhus fever should be very guardedly given, for some of the most serious and apparently most hopeless cases at the end of the second week may fall into a deep and refreshing sleep, after which there is a rapid change for the better. On the other hand, many patients who have safely passed the crisis subsequently succumb, although they may appear to be on the road to recovery.

Preventive Measures.—If the body louse is the sole medium of infection its destruction is the most effective means of preventing the extension of typhus fever. Shipley of Cambridge, England, finds that body lice cling tenaciously to the clothing, and while they may not be found on the surface of the body, the inner side of the wearing apparel next to the skin may be covered with them.

Various means have been suggested for the destruction of the body louse and various applications are advocated, a large number of which cannot be depended upon. It should be borne in mind that not only the lice but the nits must be destroyed to ensure safety, and this requires very active measures. If the clothing is worthless it is far better that it should be destroyed by incineration; otherwise steam or boiling water may be used. The latter agents may be depended upon for the destruction of this insect and nits, provided there is a proper exposure.

Treatment.—There appears to be no specific for typhus fever, and there is but little that can be done in the way of medication except by the use of remedies to relieve the insomnia or delirium, to reduce the fever and strengthen the heart. Medicine should be administered with great caution, for there is but little doubt that in many instances the chance of recovery which the patient may have had has been overcome by the injudicious use of drugs. Certain preparations have been suggested by various writers as particularly valuable in the treatment of typhus fever. The author's experience does not confirm this.

Cold applied to the head is usually grateful, and cold sponging or cold baths are frequently employed with good effects, although the latter procedure by disturbing or exhausting the patient is often contraindicated. The result in such cases should determine if this treatment is to be continued.

There is no simple measure more valuable to the patient than fresh air, and there is no reason why those sick with this disease should not, under proper bodily protection, be removed outside or placed in tents.

During the outbreak of typhus fever in New York City in 1892-1893 the hospital accommodations for this disease were inadequate and a tent service was provided in the grounds of Bellevue Hospital during the winter months. The difference in the mortality of cases treated in the hospital and in the tents soon became noticeable, being far less among

those treated in tents. It must be borne in mind that in this disease we deal with a profound systemic infection, and there is abundant and continued proof that fresh air and its stimulating and tonic effects are of inestimable value in these conditions.

What has just been said concerning the treatment of typhus fever is apparently in accord with the views of Dr. George G. Shattuck, of Boston, whose wide experience and valuable service during the outbreak of this disease in Serbia is well known. The following are extracts from a statement made by Dr. Shattuck:—

“It seems to me that the Servian epidemic confirmed the view that unhygienic surroundings and insufficient food by lowering the vitality tend to cause a high mortality.” Dr. Shattuck also believes that death occurring late in the disease is due to exhaustion associated with a gradually failing circulation and an inability to assimilate food. Dr. Shattuck is quite satisfied that medicine cannot be depended upon except in special instances, such as heart failure, restlessness, etc., and then it should be used with great care. He refers particularly to the importance of careful nursing and the probable value of intravenous injection of eight to ten ounces of a salt solution—particularly in patients who present a dried up appearance, suggesting a lack of water in the tissues.

It would seem therefore that the treatment in typhus fever relates chiefly to supporting measures, proper nourishment, careful nursing, and hygienic surroundings.

Differential Diagnosis.—Typhus fever may be mistaken for typhoid fever, measles, cerebrospinal meningitis; less frequently pneumonia, malaria, and in some instances other acute infectious diseases.

In typhus fever the invasion is abrupt, in typhoid fever it is prolonged. This is a very valuable point to bear in mind in deciding between these two diseases which most frequently call for a differential diagnosis.

In typhus fever the disease begins with a rapid rise of temperature, chill or chilly sensation, profuse headache, and early and great prostration and involvement of the mental faculties, a suffused congestion of conjunctivae and an eruption which appears on the second or third day of the disease.

In typhoid fever the temperature rises slowly and no pronounced impairment of the mental faculties usually occurs in the early stage of the disease, no injection of conjunctivae takes place and the eruption does not appear until the second week of the disease. Besides, in typhoid fever there are symptoms referable to the abdomen and the “Widal” test is available.

In typhus fever the true eruption is petechial, and generally distributed about the body, appears in one crop only, and does not disappear on pressure, whereas the eruption in typhoid fever is generally confined to the abdomen, is rose colored and papular, occurs in successive crops, and *does* disappear on pressure.

The differential diagnosis between typhus fever and measles should be easily determined, particularly after a day or two. Typhus usually affects the adult, while measles generally occurs during childhood. While

measles appearing in the adult may call for more caution in the differential diagnosis, the profuse eruption, the conjunctivitis with pronounced catarrhal symptoms and little or no involvement of the mental faculties generally indicates the diagnosis.

If care is employed, malarial fever can hardly be confounded with typhus fever, at least no longer than is necessary to observe the periodicity and to detect the plasmodium.

Meningitis, particularly in the cerebrospinal form, may for a short period in some instances be mistaken for typhus fever. However, the invasion of cerebrospinal meningitis is more abrupt than typhus fever; it usually occurs with really no premonitory symptoms; vomiting, which is a very common symptom in cerebrospinal meningitis, does not, as a rule, occur in typhus. Rigidity of the nape of the neck and opisthotonus constitute the most important signs in cerebrospinal meningitis, whereas they have no special relation to typhus fever. Furthermore, in cerebrospinal meningitis death usually takes place in from one to three days, and in typhus fever the duration of the disease is much longer. An eruption does not always occur in cerebrospinal meningitis. When present it has no definite or special form and can be easily diagnosed from that of typhus fever.

A careful examination of the chest will usually identify pneumonia, which is not a complication of typhus fever, the pulmonary involvement in the latter disease being usually confined to bronchitis.

In one fatal case under the author's observation, where the patient had an eruption which was extremely suggestive of typhus fever, the skin having in addition to the eruption a cyanosed appearance, the autopsy showed a very extended suppuration of the right kidney, from which was removed a concretion half the size of a hen's egg. While cases of this kind are rare, they should be thought of when the presence of typhus fever is suspected, particularly if there is no history of exposure to this disease and no outbreak has been reported.

BRILL'S DISEASE

In 1910 Dr. Nathan E. Brill, of New York City, who had previously (1896) referred to this subject, reported in the *American Journal of the Medical Sciences* a study of 221 cases of "an infectious disease of unknown origin and unknown pathology characterized by a short period of incubation (4-5 days), a period of continuous fever, accompanied by intense headache, apathy and prostration, a profuse and extensive erythematous, maculopapular eruption, all of about two weeks' duration,—whereupon the fever abruptly ceases either by crisis within a few hours or by lysis within three days, when all symptoms disappear."

During the following year (1911) Dr. Brill reported in the same journal further observation concerning this disease.

Dr. Brill's reports attracted the special attention of Drs. Anderson and Goldberger. In reference to this Dr. Anderson states as follows:

We were struck by the very remarkable resemblance between the disease of Brill and typhus fever as observed by us in Mexico and as observed by one of us in certain places abroad. For this reason we endeavored to gain access to a case of Brill's disease in order that we might determine if possible its relationship to typhus. A case was finally seen in the ward at Mt. Sinai Hospital and blood was drawn from the arm vein of this patient and used for the inoculation of monkeys. One of these animals after an incubation period of ten days developed a fever which reached its maximum six days later and fell by a rapid crisis fourteen days after the rise began.

Dr. Anderson concludes that typhus fever and Brill's disease are identical. He also reports that Roger Lee in a study of cases recorded in the Massachusetts General Hospital conforming to Brill's disease, covering a period from 1902 to 1912, believes that typhus fever in a mild form has prevailed in Boston and vicinity during that time. He states in his study of the records of 1,404 cases of continued fever in that institution of greater duration than seven days, 28 cases corresponded extremely closely with Brill's description of typhus fever; this gives a ratio of one case of typhus to forty-seven cases of typhoid fever.

As a result of the several investigations referred to, particularly on the part of Anderson and Goldberger, it is now generally accepted that typhus fever and Brill's disease are but different types of the same affection.

While it is true that the bacteriological investigation of Anderson and Goldberger seems to justify this belief, and although the clinical pictures of typhus fever and Brill's disease are more or less similar, and there may be no other explanation for the presence of the latter disease, there are certain points in connection with the subject which should receive careful consideration before a final conclusion is made concerning the exact relation between these maladies. It may be noted that there are some important points in connection with Brill's disease and typhus fever which are unlike. For instance, in typhus fever there is almost always an early and profound impairment of the mental faculties, whereas in Brill's disease this either does not occur or is present only in exceptional cases; furthermore, typhus fever is a dangerous and actively communicable disease involving a high mortality, whereas in Brill's disease patients rarely die and there is practically no evidence that it is communicated to others.

During the past thirty-five years there have been two epidemics of typhus fever in New York City, one during the year 1882 and the other in 1892-1893. In both epidemics the origin of the outbreak was clearly

and definitely traced to immigrants recently arriving on incoming foreign vessels; there is also definite proof that after these outbreaks subsided there were no further reported cases of typhus fever in New York City.

In Dr. Brill's report in the *American Journal of the Medical Sciences* in 1910 he states:

Clinically this disease resembles typhus fever more than it does any other disease, and I should have thought that I had offered nothing to our nosology if it had been proven that typhus fever had lost its virulence, that it was constantly present in the community, that it was not communicable, that when it was present epidemics did not occur, and that it was no longer a grave fatal disease, but that typhus fever as great Masters of Medicine have taught us, and as I have seen it, was such a conception would be unjustifiable, therefore I believe this disease is not typhus fever.

Dr. Brill and many others believe that this unknown disease has been more or less continually present in New York City as well as in other sections of the United States for many years, yet there is no recorded instance where it has taken on the form which is typical of what we know as typhus fever. Neither has it caused an outbreak of this disease and practically is associated with no mortality. In other words, Brill's disease is shown to be a benign affection and apparently not communicable.

The statement that Brill's disease and typhus fever are identical is more or less misleading and disturbing, for it indicates that a dangerous communicable disease is commonly present. On the other hand this may lead to the belief that typhus fever is not a serious menace to the public health and is likely to encourage carelessness upon the appearance of what may be called true typhus fever.

If Brill's disease does not take on the character or danger of typhus fever and so far as the public health is concerned is practically harmless, why is it not sufficient to let it be known as Brill's disease?

CHAPTER III

SMALLPOX

JOHN RUHRAH

53. Line 9 *add* after "methods.":

Laboratory Diagnosis.—In some infectious diseases the cutaneous injection of the virus will give rise to an inflammatory reaction in an animal previously sensitized. Jenner noted this, but no attention was paid to it. In 1912 Tieche found that persons who were immune to smallpox would not give a reaction with material taken from varicella cases. He suggested this as a means of differential diagnosis. His idea was that the physician could make the tests on himself or some person previously prepared with vaccine virus. He suggested heating the virus to be used in the test to 70° C. for five minutes in order to avoid accidental infection by syphilis.

Force and Beckwith have applied this method to sensitized animals and studied the effect of vaccine, the contents of the smallpox vesicles, and the chickenpox vesicles, on the skin of previously vaccinated animals. The virus is injected intradermally. On the day preceding the dose two areas about 5 cm. in diameter are shaved and clipped on the back of a previously vaccinated animal. From 0.05 to 0.1 cm. of material is injected directly into the skin. Within twenty-four hours the reaction appears and reaches its maximum the second day. There is an infiltration of the skin with redness which fades before the infiltration disappears. Typical reactions may be produced by vaccine virus or the contents of smallpox vesicles. This material can be kept for nine days at ice-box temperature and still give the reaction. Chickenpox virus does not produce any reaction in these animals. The rabbits retain their sensitiveness a long while, some of them for one year after the original vaccination. This may be used particularly in the differential diagnosis of smallpox and chickenpox and should prove very valuable in checking up the clinical diagnosis.

CHAPTER IV.

VACCINATION

JOHN RUHRAH

62. Line 23 *add* after "school.":

CULTIVATION IN VITRO

Steinhardt and Lambert, using the Harrison method of cultivating tissue *in vitro*, have made studies in rabies, vaccinia, and syphilis. They showed that there was a definite multiplication of virus in tissue cultures when corneal tissue was used in the culture medium. The multiplication was exceedingly slow and they were able to carry the growth through three inoculations.

66. Line 34 *add* after "them.":

Extensive studies have been made by the United States Public Health Service (Bulletin of the Public Health Service, 1915, p. 111), and the most careful researches fail to reveal any vaccine virus contaminated with the tetanus bacillus.

Line 41-42 *read*:

ally allotted. **Fornet suggests that sterile vaccine virus may be produced by the use of ether. A virus so treated is bacteriologically sterile and at the same time remains active for weeks.** Other methods have been

67. Line 19 *add* after "obtained.":

THE RABBIT TESTICLE METHOD.—Noguchi has been able to produce a vaccine virus free from bacteria by growing the virus in the testicle of the rabbit. The virus is first treated with ether, after the method of Fornet, to free it from bacteria as far as possible. It is then injected into the testicle, the needle being turned in various directions in order to obtain a more or less uniform distribution. The virus increases in the testicle and reaches its maximum four or five days after the injection, then remains stationary until after the eighth day, when it begins to

diminish, and at the end of five weeks it has practically disappeared. The testes are removed and ground with sterile salt solution or 60 per cent. glycerin, and this is kept as a stock emulsion. It is necessary to pass the virus through several rabbits in order to bring about an adaptation to the testes, as the strength during the first transfer may be less than the original specimen from which the strain was derived. Subsequently the activity rises until it reaches its maximum point, at which it equals that of the skin strain. The changes in the testicle of the rabbit consist of a little exudation in the interstitial spaces during the first twenty-four hours. After forty-eight hours there is a considerable swelling and induration, and this increases rapidly and the testicle becomes edematous. On the fourth day the color has become purplish red, and here and there are irregular yellowish areas of different sizes. After six days it becomes softer and the edema and filtration begin to grow less. From this time there is a rapid decrease in size, so that on the tenth day the testicle is somewhat smaller than normal.

68. Lines 3-5 *read:*

completely before the vaccination is done. **Schamberg and Kolmer** have suggested painting the vaccinated area with a 4 per cent. alcoholic solution of picric acid. This should be done forty-eight hours after the insertion of the lymph and in no way affects the success of the vaccination, but it lessens the degree of subsequent local inflammatory reaction. The skin

CHAPTER V

VARICELLA

JOHN RUHRAH

110. Line 34 *add* after "exposure." :

Children who have been in contact with the disease should be kept apart for three weeks. If the day of the first contact with the disease is known there is, perhaps, no objection to allowing the child to go about freely for the first ten days. After that, during the period in which the disease is apt to develop, the child should be kept away from other children.

112. Line 30 *add* after "marks." :

If there is any special tendency for the eruption to become infected, the pocks may be painted with tincture of iodine, which may be diluted one-half with alcohol in children with very delicate skins, or the painting may be done with a 4 per cent. solution of picric acid.

CHAPTER VI

SCARLET FEVER

J. P. CROZIER GRIFFITH

REVISED BY A. GRAEME MITCHELL

115. Lines 9-10 *read*:

ucts of degeneration. This promising investigation of Mallory **has not received** corroboration. Quite recently have appeared the in-

Line 19 (B. F.) 16 (F.) *read*:

, by Nichol and Williams **and by Farfel**. Inclusion bodies have also been found in

Line 22 (B. F.) 20 (F.) *add* after "unknown.":

Macewen found these inclusion bodies in 96 of 100 cases of scarlet fever. They are also found occasionally in measles, in the acute stage of diphtheria, and they are plentiful in typhus, erysipelas and septic conditions. The presence of sepsis, especially when caused by the pneumococcus, seems necessary for the production of inclusion bodies. Macewen has tried without success to produce inclusion bodies by the injection of streptococci and pneumococci into animals.

Line 33 (B. F.) 32 (F.) *add* after "fever.":

Kretschmer believes the disease to be in the nature of an anaphylactic reaction to streptococcus infection. The most recent important research into the cause of scarlet fever is by Mallory and Medlar. These workers have found a Gram-positive bacillus in the tonsil. The organism disappears on the second or third day following the eruption. This observation must, of course, be as yet accepted "cum grano salis."

117. Line 38 *add* after "safety.":

If it be proven that the *Bacillus scarlatinæ* of Mallory and Medlar is the true cause of scarlet fever, and that the organism disappears after the third day of the disease, then our previous conception of the period of greatest infectiousness, as well as our ideas and method of prophylaxis, will be radically changed.

129. Line 19 *add* after "manifestations.":

The serum and vaccine treatment will be found fully discussed in Volume V.

Salvarsan Treatment.—It would seem but natural that the treatment by arsenical preparations, such as salvarsan, should be attempted in scarlet fever. The Wassermann reaction is occasionally positive in this disease. Salvarsan has also been used with some success in severe necrotic inflammations of the throat, such as Vincent's angina, and in some of the protozoön diseases. Several investigators have tried this treatment which seems to have favorable influence in severe throat conditions, probably because they are contributed to by the spirochetes found in the mouth. Otherwise the medication has doubtful value.

130. Line 31 *add* after "promptly.":

As previously mentioned, salvarsan and neosalvarsan exercise favorable influence in some of these cases. The dosage varies from .15 to .45 gram of neosalvarsan. Three or four doses may be given on successive days. More than .8 gram should seldom be given in three days.

137. *Add* under "References.":

Farfel. Münch. med. Wchnschr., 1914, LXI, 437.

Glaser. Deutsch. med. Wchnschr., 1914, XL, 1760.

Kretschmer. Jahrb. f. Kinderheilk., 1913, LXXVIII, 278.

Macewen. Jour. Path. and Bacteriol., 1914, LVIII, 486.

Mallory and Medlar. Journ. Med. Research, 1916, XXIV, 127.

CHAPTER IX

MUMPS

JOHN RUHRAH

167. Line 30 *add* after "sufficiently.":

Merelli, of Pisa, claims to isolate an organism, which he calls *Micrococcus tragenus*, from the blood and from the serous fluid in the testicle from cases which were complicated with orchitis. It does not stain with Gram's method. Inoculations on small animals in the laboratory were negative, but the organism gave the agglutination tests in dilutions as high as 1 to 500. Rosenow studied an epidemic of parotitis and appendicitis, and found a coccus which produced lesions of the parotid in rabbits and dogs. The organism resembled that described by Herb.

169. Line 27 *add* after "over.":

Hess has suggested a method of protecting patients from mumps. He used from 6 to 8 c.c. of blood drawn from a donor and injected intramuscularly. This blood was taken from three groups of children: some from a patient who had just recovered and in whom there was some swelling of the parotid, some from patients recovered about ten days, and some from those who had had the disease several years previous. There were no local or constitutional reactions and none of twenty children so treated contracted mumps, although exposed to it.

172. Line 9 *add* after "demonstrated.":

George G. Smith has suggested treatment of the orchitis by means of operation, which consists of a two-inch vertical incision along the anterior aspect of the left side of the scrotum and then the opening of the tunica vaginalis. The fluid is allowed to escape after the tunica is opened over the epididymis in several places. A rubber drain is used and the scrotum tightly compressed in an Alexander bandage. The drain in a case that was operated on was removed three days later. Too few cases have been reported on to speak definitely about this form of treatment.

172. *Add* "References.":

Herb. Arch. Int. Med., 1909, IV, 201.

Rosenow. Jour. Infect. Dis., 1916, XVIII, 383.

CHAPTER X

WHOOPIING-COUGH

JOHN RUHRAH

176. Line 29 *read*:

except keeping away from individuals who have it, **unless vaccination, as mentioned later in this article, proves effective as a preventive.**

Line 39 *add* after "air.":

Whooping-cough is reportable in twenty of forty-three states in which information was secured, but in many states very little attention is paid to the law. One of the most effective means of preventing the disease would seem to be the use of some distinctive arm band or sash for all children having the disease so that they could be out of doors, but at the same time other children and nurses would be warned that the patient was a source of danger. The use of separate waiting rooms in dispensaries or separate hours for the treatment of whooping-cough cases is to be advocated, and special hospital provision should be made for cases that would be isolated satisfactorily.

178. Lines 24-28 *read*:

sened. Naegeli has suggested a simple mechanical method for relieving paroxysms of coughing, and while this is more or less generally known, it is very seldom used. The method consists of grasping the lower jaw and pulling it downward and forward after the manner used by anesthesetists. If the patient is an adult or a large child he can do this for himself. At the same time this is being done a very deep inspiration should be taken. If this is carried out when the paroxysm is impending, and most patients feel the paroxysm coming on, it will generally succeed in inhibiting the attack. With very small children who are unable to coöperate by taking a deep inspiration the procedure is not so successful. This is perfectly prac-

179. Line 27 *add* after "any.":

Schroble has suggested the use of warm baths on going to bed. The

baths should be at least $99\frac{1}{2}^{\circ}$, the child kept in it from ten to fifteen minutes and the head kept cool with cold compresses at the same time.

182. Line 37 *add* after "value.":

Papaverin Hydrochlorid may be given three or four times a day. The dosage may be one-third to one-half grain (0.02 to 0.03 gram) at ten years of age, and younger children in proportion.

183. Line 12 *add* after "undertaken.":

For full account of the use of pertussis vaccine *see* the volume on serums and vaccines. I have not had any experience as regards its use as a preventive, but from my experience with it as a curative measure I believe it would be advisable to try it out as a preventive, using doses varying from 25 to 100 million bacilli injected for several doses at rather short intervals of two or three days. The optimum dose and the best interval and value of this can only be determined by observations which have not as yet been made in sufficient quantity to justify any very exact statements. As a curative I have used 100 million bacilli injected at various intervals, not over three days being allowed to elapse unless there should have been some definite symptoms following the injection. In severe cases the injections may be given every day or every other day. Given after the first two weeks of the disease, the vaccine probably has little or no value, although this will have to be determined more definitely by future observations. Where the diagnosis can be made early in the first two weeks, the earlier the better, I believe that the vaccine possesses a very definite curative action, lessening the number of paroxysms and also the length of the spasmodic stage. Any very severe local reactions or constitutional disturbances indicate too large a dosage or too close an interval.

CHAPTER XIII

LOBAR PNEUMONIA

HENRY L. ELSNER

217. Lines 8-23 *substitute*:

The clinical classification of cases with lobar inflammation of the lungs has in the past been mainly based upon the anatomical lesions. While such a classification is of importance, as the possibilities of specific therapy become greater the need for a classification of the cases upon an etiological basis and the diagnosis of each case from this standpoint becomes increasingly great. The work of Neufeld in Germany and of Dochez and Gillespie and others at the Hospital of the Rockefeller Institute has demonstrated that the pneumococci differ in their immunological characteristics, and that upon such immunological features they may be divided into several groups. The mortality in cases due to organisms of these various groups differs, and therefore the diagnosis of etiology in each individual case becomes of considerable importance, not only from the standpoint of therapy, but of prognosis as well.

In addition to the treatment of the disease by measures directed toward destruction of the specific agent, however, treatment directed towards alleviation of the various symptoms is of very great importance.

220. Line 40 *add* after "infection.":

Miller has recently shown experimentally that the susceptibility of animals to respiratory infections is increased when they are exposed to cold, especially to sudden changes in temperature.

221. Line 36 *read*:

red alkaline solution, when the cup is emptied. **The cup, itself, should be sterilized by boiling if it is made of metal. Paper receptacles should be burned.** The burning of the

223. Line 2 *read*:

before the administration of the anesthetic. **The inhaler employed should be sterilized each time before it is used.**

224. Line 27 *add* after "necessary." :

If the patient is treated in the open air, it is quite important that arrangements be made so that the bed can be moved into a warm place when the patient is examined, the bed clothing changed, or for any reason exposure is necessary. Every effort should be made to keep the patient's body warm, and it is important to remember that not only is covering necessary, but also sufficient blankets to cover the mattress should be provided, in order that the heat may not be lost by radiation downward. An important point to be remembered in outdoor care of patients is that the nurses should be cautioned to wear sufficient clothing to guard against cold. It is not necessary to expose the nurse to undue risk in order to aid in the recovery of the patient.

226. Line 32 *add* after "used." :

The mouth, lips and nares should be carefully cleansed and albolene frequently applied to prevent dryness and cracking. The healing of herpes may be hastened by the application of spirits of camphor, followed by albolene or boric ointment.

227. Line 11 *add* after "infection." :

The application of large flaxseed poultices to the chest frequently gives complete relief from the pain. In all places where local applications are made careful attention should be paid to the condition of the skin.

Line 22 *add* after "patient." : "

With involvement of the lower lobes, pain is not infrequently referred to the abdomen, and the physician should always be on his guard against mistaking such a pneumonia with abdominal pain for an acute abdominal condition, as appendicitis. It is not impossible that both conditions may be present at the same time, as in one case seen by the writer, though, of course, this must be extremely rare.

Line 38 *add* after "gas." :

Care must be taken, however, to avoid too active catharsis, which imposes an unnecessary strain upon the patient. In most cases, after the initial cathartic, simply a soap suds enema given every morning is all that is required to keep the lower bowel evacuated.

Line 43 to **228.** Line 19 (inclusive) *substitute* :

Abdominal Distention.—This symptom is usually, but not always, an index of the patient's intoxication. When it becomes marked it may very seriously interfere with the circulation and respiratory movements. Its development should be vigorously combated, and this can best be done by very careful watching and proper treatment carried out while the condition is still slight in degree. Palpation of the abdomen is fully as important as percussion of the chest in the routine physical examination. With the slightest sign of distention the diet should be restricted and mild cathartics should be given. In the mild case peristalsis should be

stimulated by the use of glycerin suppositories. Where this is ineffectual turpentine stupes should be applied. They may be applied as rapidly as needed for twenty minutes, then omitted for twenty minutes, and again repeated. The insertion of a rectal tube often aids in the expulsion of gas. It is advisable to allow the rectal tube to remain for some time.

At the Presbyterian Hospital, New York, the following enema is frequently given with excellent results. It consists of a mixture of

Fel bovis	3 i
Turpentine	3 ii
Asafetida	3 iii
Soap suds	1-2 parts

This is retained as long as possible, and followed in one hour by soad suds enema. Care must be taken, however, not to unduly exhaust the patient by too frequent and persistent use of large enemas.

Occasionally all these methods bring little relief, and in such cases temporary improvement may follow the use of pituitrin given intramuscularly in 1 c.c. doses.

Delirium.—The delirium of the average case, *non-alcoholic*, is easily managed by occasional doses of codeia or morphia. It does not require

Line 30 *add* after “unsuspected.”:

In such cases it is often wise to give 15-30 c.c. of whisky every two to four hours, where this is not distasteful to the patient. With the first appearance of symptoms of delirium tremens 0.6 gm. of veronal should be given in the early afternoon, repeating after four hours if necessary. If this does not suffice to quiet the patient, the use of paraldehyd in 10-20 c.c. doses by mouth or 30 c.c. by rectum has been found safe and efficacious. In very severe cases it may be necessary to use hyoscin, but this drug should be employed with the greatest care, and its use limited to the occasional most extreme case.

237. Line 29 *add* after “measured.”:

This subject is treated in Vol. V, p. 9, and the reader is referred to this for full details.

247. Line 31 *add* after “cord.”:

With a more satisfactory and exact technique Porter and Newburgh have reëxamined the question of “the state of the vasomotor apparatus” in pneumonia experimentally and have denied “that the toxins of pneumonia specifically injured the vasomotor cells.” Therapy which is grounded on the theory that these are injured is for the present, therefore, not based on satisfactory experimental evidence.

Line 42 *add* after “paralysis.”:

Late reports on carefully studied autopsies, by Liebmann, E., fail to show serious degenerative changes in the heart muscle. From the point of

view of histology it is indeed doubtful whether the slight changes which have been found can be regarded as significant.

250. Line 3 read:

tone; hence for all that, **this condition calls for an agent which tends to stimulate and maintain heart action**

Line 11 *add* after "(Ortner, 64).":

An important consideration in defining the indications for digitalis administration lies in the frequent occurrence of auricular irregularities, either auricular fibrillation or auricular tachycardia (flutter). The initiation of either of these irregularities is characterized by a rapid increase in pulse rate, ranging as high as 180 or even more. A condition such as this, if permitted to proceed unchecked, may easily, in a short time, alter the future course of the disease from one with a favorable outlook to one in which the outcome is extremely grave. The onset of this complication is not confined to patients whose hearts are previously damaged, nor even to patients apparently severely toxic. It may occur in any patient. Sometimes, even if untreated, the irregularity disappears spontaneously, but it is not advisable to rely on this event. Digitalis is usually an efficient remedy for combating this condition. On account of the frequency with which these irregularities occur (12 times in 123 cases), it is suggested that digitalis be given in a prophylactic manner. There is no reason for believing that giving digitalis disposes to the onset of an irregular heart. But we have observed the onset of auricular fibrillation accompanied not by a rise but actually by a fall in ventricular rate, when the patient was previously digitalized. If treatment can be begun early in the disease, 1.0 gram of digitalis leaves (or the equivalent) may be given during 24 or 48 hours in divided doses (0.5 gram each day), and the patient then be considered digitalized. If subsequently an irregularity of the nature described occurs, as much more digitalis as is required may be given. The ventricular rate will almost invariably fall. If the indication arises soon after the initial administration is terminated, 0.5 gram a day may be given until the ventricular rate is lowered. In this method of treatment emphasis must be laid on the extreme danger of giving subsequently either digitalis or strophanthin intravenously; these drugs may be given by mouth only. It is important to call attention to the fact that under all circumstances it is desirable to know what the cardiac mechanism of the patient is, and to keep informed of this throughout the course of the disease, and especially promptly if an alteration in rate suddenly occurs. The electrocardiographic method is especially recommended for obtaining this information whenever, as in hospitals, it can be employed. It will be more difficult to obtain this evidence by other graphic methods.

In the presence of partial heart block it is probably unwise to admin-

ister digitalis. During the course of the disease, however, the occurrence of a partial block is probably exceedingly rare. If the block is complete, giving digitalis can do no harm.

The statement of Hare "that digitalis is less powerful in its effects in pneumonia than with valvular lesions, that with the infections associated with fever and myocardial degeneration it does not produce its full physiological effects," is probably incorrect. The observations of Cohn and Jamieson, based on a study of the effect on the auriculoventricular interval and on the behavior of the *T* wave of the electrocardiogram, as well as the reaction of the heart in auricular fibrillation and tachycardia, indicate that digitalis acts in pneumonia precisely as it does on the heart in heart disease. And the inference may be drawn that the other actions of digitalis on the heart, the blood vessels and the kidneys are exerted in pneumonia as they are under other circumstances. There need, therefore, be no separate indications for its use in this disease, apart from those already mentioned.

A reliable digitalis preparation causes increased tone of muscular tissue generally, most conspicuously in arterial and heart muscles; it increases the strength and duration of the ventricular systole, and causes a small rapid pulse and cardiac dilatation.

253. Line 25 *add* after "standardized.":

It is important to notice that Hatcher states "that the amorphous strophanthin varies somewhat in activity, but so far we have found no variation in the activity of the crystalline." Boehringer's strophanthin is an amorphous preparation. The degree of variability is not given by Hatcher, but experience has shown that the strength of this preparation may vary within unsafe limits. Caution is therefore urged in its use, especially when it is given repeatedly. It should under no circumstances whatever be given if digitalis has been employed any time within at least a week.

255. Line 8 *add* after "it.":

This vexed question of the influence of pneumonia on the blood pressure has again been reviewed and studied by Newburgh and Minot. They have included a consideration of Gibson's rule. They state, among their conclusions, (1) that "blood pressure measurements in pneumonia cannot be used as a basis for treatment"; (2) that the "prognostic inferences based on the relation of the level of the systolic pressure curve to the pulse curve (Gibson's rule) are wrong more often than they are right in this series"; (3) that "low systolic pressures are not invariably of evil omen."

257. Line 25 *add* after "disease.":

During the height of the disease if the patient is annoyed by frequent coughing, especially if this is accompanied by pleuritic pain, it is wise

to use small doses of codein (32 mg. or $\frac{1}{2}$ gr. every four hours if necessary). In convalescence where the sputum is abundant, more rarely scanty, inhalations of compound tincture of benzoin or creosote two or three times a day often afford relief.

Line 30 *read*:

of ethereal stimulants **and** adrenalin **and** regular use of digitalis, caffein,

260. Lines 26-27 *read*:

by digitalis or without. At times this is accompanied with **sinus irregularity, partial heart block**, and occasionally extrasystoles. With bradycardia the pulse

261. Lines 27-36 *substitute*:

Gangrene of the Lung.—The advice of the surgeon should be obtained as early as possible after diagnosis is made. It is usually a fatal complication. The patient may be made more comfortable and less repugnant to those caring for him by internal administration of terebene and by the inhalation of balsamics. Eucalyptol, oil of sylvestrian pine, and compound tincture of benzoin are particularly useful for this purpose.

262. *Add* under "References.":

Porter and Newburgh. Amer. Jour. Physiol., 1914, XXV, 1-14.

Hatcher, R. A. Jour. Amer. Med. Assoc., 1910, LIV, 1050.

Liebmann, E. Untersuchungen ueber die Herzmuskulatur bei Infektionskrankheiten; (2. Mitteilung) Ueber Veränderungen der Herzmuskulatur bei Kruppöse Pneumonie; Deutsch. Arch. f. klin. Med., 1915, CXVIII, 190-213.

Newburgh, L. H., and Minot, G. R. Arch. Int. Med., 1914, XIV, 48-55.

CHAPTER XIV

DIPHTHERIA

THOMAS DARLINGTON

REVISED BY BINFORD THORNE

267. Line 5 *add* after "defects.":

In institutions for the care of children cultures should be made from both the nose and throat of all new inmates on admission, to detect a possible carrier.

If diphtheria bacilli are found, the child must be kept isolated until a virulence test is made. If the bacilli are virulent, further isolation until the child's nose and throat are free from them is absolutely necessary.

Line 6 *read*:

All cases of diphtheria should be quarantined **until cultures from both nostrils and the throat show no diphtheria bacilli on two successive days.** In this disease much

268. Line 8 *add* after "antitoxin.":

In institutions, asylums and schools where the disease exists and when it is present in the neighborhood, the Schick test can be used to detect those who are susceptible. This test consists of the intradermal injection of 1/10,000 of the minimum fatal dose, for a guinea pig, of diphtheria toxin. After twenty-four to forty-eight hours there occurs, in those who are not protected, a local reaction at the site of injection consisting of redness and infiltration which subsides, leaving a pigmented and slightly scaling spot. A negative reaction always indicates the presence of sufficient protective bodies. A positive reaction does not exclude their presence. As some people will show some inflammatory reaction, all who show a positive reaction should be immunized. The ages of those exposed is quite important, as Schick and others have shown that susceptibility to diphtheria is greatest between two and five years of age, only about 40 per cent. showing antibodies.

The immunity conferred by the injection in diphtheria antitoxin lasts only about two weeks. In institutions it is advisable to obtain a more lasting immunity. This can be done by injections of a mixture of diphtheria toxin and antitoxin. Park says a satisfactory combination is $\frac{1}{2}$ c.c. of strong toxin containing approximately 100 fatal doses for a guinea pig, with approximately 20 per cent. more antitoxin than is sufficient to neutralize this.

This injection usually confers an immunity which lasts more than a year. Three months after the injection another Schick test is made and those in whom it is positive should receive another injection of the toxin-antitoxin mixture.

269. Line 40 *add* after "dose.":

It is advisable to give sufficient antitoxin at the first injection to cure the case. The greatest benefit is derived from this first injection, and the pain and excitement caused by its repetition should be avoided if possible.

270. Lines 1-13 *read*:

uvula, or to the posterior wall of the pharynx, should receive **15,000** units as an initial dose. Cases similar to these with the additional involvement of the nose or nasopharynx should receive an initial dose of at least **15,000** units to **20,000** units. Septic cases, ill five to seven days with necrotic membrane of extremely foul odor, with tendency to hemorrhage from the nose or pharynx, and petechial spots in the skin, can be given enormous doses, up to **30,000** units. Larger doses have been **given**.

All croup cases should receive at least **12,000 to 20,000** units, and if the pharynx is involved with the larynx the dose should be increased to **15,000** units.

It **may be advisable** to repeat the dose. The indications for this are:
1. If, after **48** hours, the false membrane is spreading, or does

Line 30 *add* after "precautions.":

Park has shown that after subcutaneous injection the antitoxin content of the blood increases rapidly for the first twenty-four hours and then more slowly for the next twenty-four hours, and no more increase after the first day. When injected intramuscularly the absorption is much more rapid than with subcutaneous injection; after four or five hours it being from five to twenty times; in seven to eight hours from three to ten times and after twenty-four hours at least five times as great.

When injected intravenously the maximum effect is obtained at once. After eight hours it begins to fail. From the above we see the ideal method is the intravenous, using a prominent vein at the bend of the elbow. If the physician has not the requisite skill or the veins are too small the injection should be made deeply into the muscles of the back or the gluteal region.

Lines 36-37 read:

When injected subcutaneously the site of choice is at or about the level of the nipple line. **Subcutaneous** injections in the arm, leg, or

CHAPTER XVI

SEPTICOPYEMIA

GEORGE DOCK

288. Line 35 *read*:

tiation of germs must be made, as in the case of germs of the colon **and streptococcus** groups.

CHAPTER XVII

ACUTE ARTHRITIS

Including Rheumatic Fever

THE PATHOGENESIS OF ARTHRITIS

ERNEST E. IRONS

Progress toward a satisfactory understanding of the pathogenesis of arthritis has been retarded by the relative obscurity of the etiology of some types, and, in other forms whose etiology has been better known, by ignorance of the mechanical factors which lead to the lodgment and growth of bacteria in joints and other structures of the body. Modifications in our views as to the presence of bacteria in the blood in disease have had an important influence on our conceptions of the mechanism of production of arthritis. Whereas formerly the presence of bacteria in the blood was regarded as of serious significance, indicating usually a terminal event in the course of sepsis, we now know that in diseases such as typhoid fever and pneumonia bacteriemia occurs regularly, and that in other diseases such as the complications of gonococcal infection, in which the organisms were formerly thought to be confined to the original site of infection, a demonstrable though intermittent bacteriemia occurs. By studying a series of infections of the same etiology which exhibit decreasing degrees of virulence it is readily possible to find instances in which cultural examination of metastatic lesions in joints demonstrates the presence of viable organisms which must have reached the joint by way of the blood, but whose presence in transit in the blood excited no symptoms suggestive of bacteriemia. In such cases the joint lesion can no longer be explained on the theory that it is due to toxins formed at a distant point and acting in some unexplained way on the tissues of a particular joint. The course of the lesion thus initiated will depend on the viability and vigor of growth of the bacteria in the embolic focus on the one hand, and on the degree and nature of reaction of the tissues

of the joint on the other. The bacterial embolus reaches some portion of the periarticular structure and a minute focus is formed either in the more superficial portions of the joint, or deeper in the capsule, or in the tissue underlying the synovialis. In the latter case the layers of cells of the synovialis become swollen, and at the point of greatest damage desquamation of the altered cells of the synovial surface occurs. This irritation may cause a rapid increase in synovial secretion with resulting distention of the joint. The effusion may be sterile, or it may contain the invading organism if the latter has passed from the subsynovial focus through the damaged tissues of the synovialis. If the bacterial embolus lies at a point more distant from the synovial surface, there may be but little or no involvement of the synovialis, the lesion presenting the clinical features of a peri arthritis. The relatively avascular joint offers conditions of oxygen tension and of protection from the antibacterial forces of the host which differ from those in the blood, and in so far as these conditions favor either the growth or the destruction of the organism, they will influence the course of the arthritis.

Improved bacteriologic methods have yielded much new information as to the sources of the bacteria whose entrance into the blood stream is first evidenced by embolic phenomena. The bacteriemia may be due to, and a part of, the primary disease, as in pneumonia or epidemic meningitis, or it may arise through the invasion of the host by secondary infecting organisms, such as the streptococcus or staphylococcus, as in scarlet fever or variola. In the acute arthritis of focal infection, the primary disease in tonsil or elsewhere may occasion no remark, the first evidence of invasion being the local disturbance at the site of the embolism.

In considering acute arthritis it is important to bear in mind that in an infection of a joint by an organism there are several factors which determine the character of the resulting lesion.

There are certain peculiarities of the organisms themselves which determine the type of lesion, experience teaching that one organism is likely in the majority of instances to produce suppurative lesions while another usually gives rise to nonsuppurative processes. Thus, of a number of joint lesions arising in streptococcal sepsis we expect a larger proportion to become suppurative than of a like number of joint lesions developing in gonococcal sepsis. At the same time we know that suppurative arthritis, and even suppurative myositis, may exceptionally be caused by the gonococcus, and that, on the other hand, arthritis due to streptococcal infection often subsides promptly without formation of pus. Our conception of the clinical picture of each form of arthritis is based on what usually happens, but here as in all other medical problems it is important to remember the exceptions as well as the rule. The behavior of an organism is affected no doubt not only by its own average characteristics and powers of growth in a host of given species, but also by peculiari-

ties of food supply, and tissue reactions afforded by the individual host of the species. Varying degrees of susceptibility to infection on the part of different individuals is a fact universally recognized in medicine. This variable susceptibility to the attack of an invading organism not only determines whether invasion shall occur at all, but must also exert an influence on the type of lesion produced after successful invasion has taken place. The activity of the resistant forces of the host, the degree of protection afforded to the invader by the different tissues in which it finds itself, and the condition of the tissues with respect to previous injury and daily trauma of use, will thus influence the subsequent course of the local contest between invader and host, and so determine the type of lesion whether it is to be transient or chronic, rapidly healing or suppurative.

Thus there are a number of factors which enter into the formation of the clinical picture of acute arthritis, whether produced by various organisms, or by the same organism in persons of varying general or local susceptibility. In general the type of organism seems to be more important than individual susceptibility of the human host in determining the course of the arthritis, and so from the clinical type of the arthritis one may draw some, though perhaps limited, deductions as to the probable bacterial etiology of the infection.

Other associated lesions and diseases, either preceding or accompanying the arthritis, such as scarlet fever, angina, gonorrhea, or sepsis, frequently furnish the clew to the probable nature of the invading organism. In other instances the source of the infection is local, small, and often less evident, so that a more careful examination and consideration of all the possible sources of infection are necessary before the real cause can be determined. Arthritis arising from such local infections is often recurrent, and through repeated attacks the joints sustain more permanent injury, the arthritis then passing into one of the several forms of chronic joint disease. But such cases are often seen during the first attack, and then call for a differential diagnosis from the other possible causes of acute arthritis. In these cases, even more than in the arthritis associated with acute infectious diseases, a correct etiologic diagnosis is important to the patient; for if the source of his infection, such as an abscess in the tonsil, can be found and removed, he will be spared the discomfort of subsequent attacks and the dangers of prolonged or permanent disability of the chronic forms of joint disease.

Bacteriologic examination of the evident sources of infection, and of the synovial effusion when this can be obtained, affords valuable information as to the cause and also as to the prognosis and treatment of the joints involved. But a lack of facilities for extensive bacteriologic studies by no means precludes the possibility of a successful search for the cause of acute arthritis, even in the large group of patients in whom other

characteristic symptoms of clinically recognizable infectious diseases are absent. The studies of recent years on the causes of arthritis, while greatly assisted by newer and more incisive methods of bacteriologic study, have been aided to an equally large extent by improvement of clinical methods of examination, such as the X-ray, and by the renewed recognition of the self-evident fact that every patient should be submitted to a painstaking and minute physical survey.

The old surgical maxim that it is the closed process from which absorption of infection is most likely to take place has been again brought to the fore. Equally important is the recognition of the fact that the site of the initial infection need not be a large one. Bacteria may pass from very small and unnoticed foci into the blood stream and produce multiple arthritis as well as other lesions in distant parts of the body.

CLASSIFICATION OF ACUTE ARTHRITIS

While there is still much to learn of the pathogenesis of acute arthritis, a convenient working classification based on etiology may be formulated even in the imperfect state of our present knowledge.

The large majority of cases of acute arthritis fall into one of the following three large groups:

1. Acute arthritis associated with the infectious diseases and caused (a) by the organism responsible for the primary disease, as in pneumonia, epidemic meningitis, and streptococcal sepsis; and (b) by secondary invading organisms, such as the streptococcus in scarlet fever.

2. Acute arthritis associated with local primary infections, in which the source of the infection may be clearly evident from coincident clinical symptoms, or so obscure that the only symptoms are those of the joint lesions.

3. Acute arthritis of rheumatic fever.

Whether the arthritis will heal, leaving functionally intact joints, or whether there will remain permanent anatomic changes which will be increased by recurrences of the acute process in the joints will depend on the combination of circumstances in the individual case, including the nature of the infecting organism and the opportunities for reinfection, together with the many factors which modify the reaction of the joint tissues to the injury.

Other forms of acute arthritis less commonly encountered are those due to external trauma with or without perforation of the joint, the arthritis of gout, the arthritis met with in the hemorrhagic diseases, scurvy, and serum disease, and the arthropathies associated with nervous diseases, such as tabes, in which the onset may be sudden and the joint present the appearance of an infectious arthritis. The arthritis occurring with the

purpuras is associated with fever and other symptoms suggestive of an acute infectious process, and further studies may place these forms of joint disease close to rheumatic fever, with which they have many points in common.

ACUTE ARTHRITIS COMPLICATING THE INFECTIOUS DISEASES

In the acute infectious diseases of known etiology in which the specific organism is present in the blood, arthritis occurs as an occasional complication.

The pneumococcus, which usually localizes in the lung and gives to the infection the well-known clinical characteristics which we recognize as lobar pneumonia, may also invade the joints, and pneumococcal arthritis is an occasional complication of pneumonia, or of pneumococcal sepsis in which pulmonary symptoms may be absent. Likewise, acute arthritis is occasionally seen in epidemic meningitis, and the meningococcus can be demonstrated in the purulent exudate. In Malta fever arthritis is frequent, and occasionally it is seen in typhoid fever. In these the suppurative or nonsuppurative lesions in joints may be accompanied by metastases elsewhere,—in serous membranes, bones, lymph nodes,—or the joint inflammation may be the only apparent gross lesion.

In erysipelas and in streptococcal sepsis the joints are invaded with somewhat greater frequency. In tuberculosis, besides the usual chronic tuberculous arthritis, there occurs more rarely an acute arthritis often of the larger joints, as the knee or ankle, which in the first days of its appearance suggests the arthritis of the acute infections. Some of the acute arthritis seen in tuberculosis is no doubt due to secondary bacterial infection, but in some instances tubercle bacilli have been demonstrated in the joint lesions.

In syphilis an arthritis in which acute exacerbations occur is sometimes seen, particularly in the subjects of congenital syphilis.

The exanthemata are often complicated by secondary invasions of pyogenic bacteria, which localize in joints, serous membranes, bones, and lymph nodes. It is, of course, possible that the etiologic infectious agents of the exanthemata, as well as the pyogenic bacteria, may invade the joints and share in the pathogenesis of arthritis, but of this we have no direct knowledge. Numerous instances of secondary arthritis are noted in scarlet fever, in which streptococcal bacteriemia with metastases in joints is frequent. Severe attacks of measles also may be complicated by secondary pyogenic infections involving bones and joints.

Streptococcal infections of the throat and nasal passages, which in recent years have occurred in epidemics in most parts of this country, arising in some instances from infected milk supplies, in other in-

stances apparently by contact, have exhibited a remarkable number of complications, among which have been instances of arthritis. As in other streptococcal infections, many of these joint lesions heal after a short period of activity, without the formation of purulent arthritis, but a few present severe suppuration requiring drainage. Some patients who exhibit complications, such as sinusitis, otitis, or peritonsillar abscess, later, after the acute symptoms in the throat have subsided, suffer from a new invasion, with multiple arthritis, which may be recurrent. Such instances constitute the more acute forms of arthritis which result from a type of focal infection to be referred to later. The occurrence of arthritis and other metastases in some persons, and the absence of lesions beyond the local infection of the mucous membranes in others, all of whom are subjects of infection by the same or closely allied organisms in the same epidemic, again emphasize the importance of individual variation in susceptibility and resistance to infection.

TREATMENT

The treatment of this type of acute arthritis is largely symptomatic. In many instances the arthritis is the only evidence that bacteria have been present in the blood stream. The nature of the primary disease will usually give a clew to the etiology of the arthritis.

In addition to general supportive treatment suited to the disease in which the arthritis occurs, measures must be taken to relieve pain in the affected joints. Hot applications are valuable. Immobilization, partial or complete, depending on the degree and site of joint involvement, should be accomplished by means of pillows, sand bags, bandages, or splints. Whatever the method employed, it should never interfere with the daily observation of the affected joint. When effusion occurs, it is often wise to aspirate the joint; if the effusion is large, the removal of fluid gives great relief to the patient. The early detection of purulent arthritis and the institution of drainage may be the means of saving the joint from irreparable damage, while also removing from the patient one source of intoxication. It must be remembered, however, that even in the arthritis due to invasion by pyogenic organisms the joints may heal without suppuration.

There are instances of severe streptococcal infection in scarlet fever, in which the patients become progressively more and more toxic with multiple suppurating joints, but this extreme picture is not the rule, the majority of cases of streptococcal arthritis healing without the necessity of surgical interference.

In the diagnosis and subsequent care of this type of acute arthritis, the possibility of acute osteomyelitis must always be borne in mind. Osteomyelitis adjacent to a joint may simulate arthritis, and sometimes

arthritis and osteomyelitis occur together. In addition to the data from physical examination, repeated röntgenograms are of great value in arriving at the diagnosis.

Meningococcal arthritis, which occasionally is seen following epidemic meningitis, has been successfully treated by aspiration of the joint and injection of antimeningococcic serum.

Syphilitic arthritis usually yields promptly to antisyphilitic treatment, including iodids and mercury.

ACUTE ARTHRITIS ASSOCIATED WITH LOCAL INFECTIONS

In general the acute arthritis arising from localized infections does not differ in the mechanism of its production from the arthritis occurring in certain of the acute infectious diseases in which bacteriemia is regularly present.

While the arthritis is likely to occupy the center of the clinical picture, the general symptoms of infection may vary greatly in degree. The local lesion which formed the infection atrium may be clearly evident in one case; in another it may be entirely hidden. Gonococcal arthritis affords a good example of the range in the degree of the arthritis and of the symptoms of general infection. In one patient multiple arthritis may suddenly appear during a chronic gonococcal infection, with scarcely any fever or general symptoms of infection; in another patient, the arthritis may be accompanied by symptoms of severe sepsis, high fever, and a readily demonstrable gonococcemia. In the latter form the arthritis might be regarded as properly belonging in the previously described group, which includes cases arising in the course of acute general infections, but in its more common form the prominent features of gonococcal arthritis are the arthritis and the local genital infection.

But in addition to the evident local infections, such as abscesses, suppurating wounds, or gonococcal infections which have long been recognized as portals of entrance into the blood stream of organisms which localize in joints, the studies of recent years have demonstrated sources of infection entirely hidden from casual examination, giving rise to no local disturbance sufficient to suggest their presence. The discovery that from such relatively small and hidden sites bacteria can pass into the blood stream and lodge in distant structures of the body such as those of the joints, eyes, muscles, or tendon sheaths, and there set up lesions affording the first evidence that infection is present, is of the greatest importance in the diagnosis and treatment of these disabling affections, and has facilitated the understanding of the entire subject of lesions of joints, muscles, nerves, and special organs of the body.

During the cold and wet seasons a strikingly large number of the

patients in the medical wards of hospitals, particularly of the large centers of population, are found to be suffering from some form of arthritis. Some of these present on admission the clinical picture of rheumatic fever, and the subsequent course confirms the diagnosis. Others who on entrance show symptoms of rheumatic fever, after a few days fail to exhibit the migratory character of joint lesions, or in other aspects early lead the physician to question whether after all they may not be suffering from some other form of arthritis.

Rheumatic fever itself presents many variations in its course, and there is no one absolutely diagnostic symptom. Nevertheless, cases of rheumatic fever present a rather characteristic complex, to which many of these other cases do not conform. The latter constitute to a large extent the acute-arthritis group consecutive to focal infection. Occasionally acute arthritis conforming in almost all essentials to rheumatic fever is met with following local infections of the extremities, such even as a subungual streptococcal infection.

While rheumatic fever is a very common disease, there seems to be no doubt that many cases diagnosed as rheumatic fever are in reality types of acute multiple arthritis arising from chronic infections in alveolar abscesses, chronic tonsillar abscesses, prostatic infections, nonvenereal as well as gonococcal, the acute infection developing in the patients after prolonged exposure to debilitating influences, such as cold, wet, poor food, or severe exertion, without sufficient opportunity for recuperation.

Cutaneous lesions, erythematous and nodal, are seen with the arthritis arising from focal infection as well as with that of rheumatic fever. Acute or recurrent tonsillar infection is found associated with erythema nodosum and arthritis, and the same streptococcus has been isolated from all three sites. In ulcerative endocarditis of the subacute or chronic type due to streptococcus viridans, subcutaneous and intracutaneous tender nodes appear, especially in the finger tips, and they may be accompanied by acute transient arthritis. In all these forms of joint diseases it would seem more important to emphasize the element of bacterial embolism occurring in the course of a bacterial invasion of the blood, now with one, now with another organism, rather than attempt to ascribe all clinically similar lesions to one specific organism.

The conditions which determine the type of lesion, whether in joint, skin, or muscle, whether slight and temporary or chronic with pronounced inflammatory edema or frankly suppurative, are probably many and concern on the one hand the general type or species of the invading organism, as well as its finer peculiarities and growth requirements, and on the other hand the degree of resistance of the tissue of the host, both local and general. It is the combination of these circumstances, which may be expressed in relative terms of the invasive power of the organism and of the resistance of the host, that in any given case determines the

type of lesion produced. It is not surprising therefore that clinically similar lesions may be found in a variety of infections. At the same time it must be remembered that under approximately the same circumstances a given organism is likely to behave in a more or less constant manner, a fact which insures a fairly constant clinical picture in some infections, but does not prevent exceptions when the complex of circumstances varies, and does not prevent variations in the severity or types of complications during different epidemics.

TREATMENT

The first consideration in the treatment of acute arthritis from whatever cause is the comfort and safety of the patient. Relative or absolute rest, the protection of inflamed joints by bandages, cotton pads, or by various degrees of fixation by splints, the giving of analgesics when pain is severe, appropriate diet depending on the degree of the coincident general infection, and appropriate surgical treatment when excessive effusion or suppuration occurs, are measures which are to be employed in acute arthritis without regard to its cause.

Every patient suffering from arthritis should receive a thorough examination. This should include exploration of all possible sources of infection,—the sinuses by direct examination and by transillumination and röntgenograms; the teeth by direct examination and röntgenograms followed by expert dental consultation; the tonsils, particularly those which are more or less buried by adhesions and scar tissue, by careful exploration; the prostate in men and the pelvis in women;—and other routine physical examinations and investigations of the blood and urine. To many, these suggestions will seem unnecessary; to others they will appear to impose an excessive labor without hope of reward commensurate with the effort involved.

The temporary relief obtained by symptomatic treatment should not prevent further efforts to arrive at an etiologic diagnosis, for apart from the desirability of thoroughness of examination in general, such a search is not infrequently rewarded by the discovery of some condition which permits of the application of more specific, and perhaps rapidly curative, measures.

It may be urged that because the treatment of acute arthritis is largely symptomatic whether the arthritis occurs in rheumatic fever or in other forms of infection, the question of the exact etiology is more academic than practical. This position is not tenable, both because it is subversive of true progress in medicine and because by taking it the physician misses many opportunities for service to the patient.

When patients are thus carefully examined and relieved of the chronic infections, wherever found, the results in hastened cure of the arthritis

and in the freedom from recurrence are often remarkable. By no means all patients proceed to rapid and complete recovery, but the proportion who respond to treatment directed against the cause of the illness, when this can be found, renders a faithful trial of these measures well worth while in all cases.

Some of the failures of treatment based on this search for the source of the infection have been due to the incompleteness of the examination. Multiple foci of infection are surprisingly frequent in such patients. It is not sufficient to stop the search on the finding and removing of one infected area; the examination should be continued until no further infections can be demonstrated.

TREATMENT OF GONOCOCCAL ARTHRITIS

Gonococcal arthritis is so frequently met with that, though its treatment is largely an application of the principles already stated, some mention of their application in this particular form is desirable.

Contrary to statements in some of the older texts gonococcal arthritis is almost always polyarticular. An analysis of 50 cases by Cole showed polyarthritis in all but 3, with an average of six affected joints to the patient. While the arthritis is multiple at the onset, it often persists in some one joint, usually one of the larger joints, such as the knee, and, as Cole suggests, the larger number of monoarticular cases seen on surgical services is probably dependent on the stage of the illness at which the joints are seen.

At the onset of gonococcal arthritis following an acute gonorrhea, the urethral discharge may temporarily disappear, but in the majority of cases some evidence of the local genital lesion is present. In attempting to correlate the history or presence of an old gonococcal infection with an active arthritis, it is important to remember that while the probability is that the two are etiologically related, it is quite possible for a patient who previously has had a gonorrhea to suffer from arthritis arising from some other cause. (For a further discussion of the diagnosis of gonococcal arthritis, *see* Vol. V.)

The systemic effects of gonococcal infection are remarkably variable. Some patients suffer but little inconvenience aside from that occasioned by the arthritis; the fever is only slight and the appetite remains good. Others are very ill, presenting the symptoms of a severe sepsis. These patients sometimes lose weight and strength rapidly, and may develop a high grade of anemia. In general, however, anemia in gonococcal arthritis is not pronounced. When pain is severe, analgesics such as are given in rheumatic fever (q.v.) are indicated. In severe cases care must be taken to maintain nutrition so far as possible by an easily digested and nourishing diet.

The local treatment of the joints of gonococcal arthritis is directed to the relief of pain and the maintaining of relative rest of the joint. Partial immobilization by cotton held in place by bandages reinforced by cardboard or more rigid splints may be sufficient to relieve the pain. A molded plaster splint is often serviceable, but whatever method of immobilization is used, care must be taken not to leave the joint completely fixed too long in one position, lest adhesions produce a permanently stiff joint. For this reason the partial splints, which frequently need readjustment, are preferable to the plaster cast.

In the larger joints, especially the knee, where effusion is frequent, distention of the joint capsule is often responsible for the pain. Aspiration of the joint, performed under careful asepsis, is a safe and advisable procedure, which usually gives prompt relief.

Bier's method of hyperemia produced by a few turns of elastic bandage above and below the joint, drawn only sufficiently tight to produce redness of the skin, leaving the joint surface warm, may be applied for two or three hours at intervals during the day.

In the more chronic types, baking and other forms of hot applications are beneficial. In the infrequent cases of frankly suppurative arthritis due either to the gonococcus alone or more often to a secondary infection by other pyogenic bacteria, surgical treatment by irrigation is indicated. Surgical measures further than aspiration are not usually necessary in the ordinary acute arthritis.

Local treatment of the source of the infection in the urethra and prostate after the subsidence of the acute symptoms is important. Massage of the prostate and the correction of strictures should be carried out.

Antigonococcic serum has been used extensively, but its value is extremely doubtful. Gonococcal vaccines given subcutaneously have appeared to be of some value in subacute arthritis in hastening recovery. There is at present some question as to whether the effects produced by their injection may not be in part nonspecific, such as are now known to follow the injection of any foreign protein. (For a further discussion of gonococcal vaccines *see* Vol. V.)

ACUTE ARTICULAR RHEUMATISM (RHEUMATIC FEVER)

Confusion in the use of the term "rheumatism" has arisen through lack of knowledge of the etiology of the various types of arthritis, as well as through the further misuse of an already vaguely defined term to describe almost any condition presenting symptoms suggestive of the pain or disability popularly recognized as attendant on arthritis. With increasing knowledge of the pathogenesis of arthritis it has been possible gradually to define groups of arthritis in accordance with their several

microbic and other causes, so that there is at present no further excuse for continuing the loose use of the word rheumatism.

Following the usage of those who have given the best thought to the subject, this discussion confines the term "rheumatism" to the disease known also as rheumatic fever, or acute articular rheumatism, a malady which the studies of years stamp as a fairly well-defined clinical entity. It has been urged in the interest of accuracy that a word so badly abused as "rheumatism" might well be discarded altogether, but until there is a general agreement as to the etiology of the disease the term "rheumatism" used in this restricted sense will give good service.

Notwithstanding the almost universal recognition of rheumatism as a specific disease, until its etiology has been admitted as finally and conclusively proved a brief and yet satisfying definition is difficult or impossible. In the more common form seen in young adults, the sudden onset often following exposure, with fever, acute polyarthritis with swelling, redness, and pain, involving large and also, perhaps to a less extent, the small joints, the subsidence of arthritis in joints first involved with rapid invasion of new joints, the sweating, the rapidly developing anemia, the frequent complications of endocarditis and pericarditis, and the tendency to relapse with renewal of the symptom complex are quite characteristic. A preceding or initial pharyngitis or tonsillitis is frequent.

Variations from this type, in which the arthritis is much less marked, the febrile symptoms less severe or the course less stormy but more chronic, are often noted. In children the disease may pursue a smoldering course with occasional slightly marked febrile attacks and anemia, and while joint symptoms are scarcely recognizable, injury to heart valves progresses. Here the rheumatic nodes along tendon sheaths, particularly in the palms and about joints, described by Cheadle, may give a clew to the nature of the illness. These fibrous nodes are not peculiar to rheumatism, however, being found in other infections having a chronic course and low virulence. Chorea also is so frequently associated with rheumatism, either antecedent to or following the attack, as to lead to the view that the two diseases may have a common cause.

ETIOLOGY

That rheumatism is an infectious disease seems evident from the symptoms and course, which in general resemble those of other diseases of known infectious etiology. The occurrence of unusual numbers of cases of rheumatism in an epidemic fashion, as described by a number of writers, also suggests an infectious cause, as does to a less degree the incidence of the disease in several members of a family.

A number of views have been held as to the nature of the infectious agent in rheumatism. Some have held that it is multiple, including the

staphylococci and streptococci found in other infections, but which exhibit modified degrees of virulence. The theory of a "modified pyemia" expresses somewhat the same view. Poynton and Paine isolated a small diplococcus from cases of rheumatism, which they called "diplococcus rheumaticus." In cultures it occurs in pairs or short chains. Previous investigators had isolated similar diplococci, and the occurrence of the diplococcus in the blood, joints, and subcutaneous nodes in rheumatism has been confirmed by subsequent studies of Poynton and Paine and their associates, and by others.

Inoculated into animals such as rabbits or monkeys, this diplococcus has produced joint and cardiac lesions resembling those of rheumatism. There seems but little question that the diplococcus rheumaticus is a cause of rheumatism, but to prove that it is *the* cause is a matter of more difficulty. With improved cultural methods, particularly the use of tall dextrose agar tubes in which varying degrees of oxygen tension were afforded, Rosenow was able to obtain the diplococcus from the blood or joint fluid in 16 of 18 cases of rheumatism cultured. Cultures must be made early in the disease, usually within the first two or three days, in order to obtain organisms. On the one hand, the production of joint and cardiac lesions in animals by inoculations of the diplococcus does not, of course, afford final proof of its causal relation to the disease, and on the other hand, the fact that joint and cardiac lesions follow the inoculation of animals with various strains of streptococci or pneumococci need not by any means disqualify the experimentation with the diplococcus rheumaticus as a link in the chain of etiologic evidence. Nor does the occasional finding of other organisms, such as bacilli, staphylococci, or streptococci, in cultures from patients with rheumatism present a valid argument for a multiple etiology; for, with the increasing frequency and improved technic with which cultures from blood and tissue are being made, it has become evident that in many diseases bacterial invasion of the blood by organisms clearly not etiologically related to them is a common occurrence.

While it is advisable still to maintain an open mind as to the etiology of rheumatism, the evidence is growing that the diplococcus or streptococcus rheumaticus of Poynton and Paine must be seriously considered as a cause of the disease.

PROPHYLAXIS

The low immediate mortality and the frequency of recurrences of rheumatism afford opportunity for the employment of measures to prevent subsequent attacks, and the serious consequences of the complications, especially those involving the heart valves, impose an added responsibility upon the physician to do all in his power to avoid renewed activity of the infection, which if continued will sooner or later lead to invalidism.

In the case of those who have suffered from previous rheumatism severe exposure to cold or wet must be avoided. The lesser degrees of exposure, which usually produce no noticeable effects in the average child, may be sufficient to precipitate an attack in one who has recently suffered from the disease. Attempts to guard the child from exposure should not, however, lead to undue confinement; abundant opportunity should be allowed for outdoor exercise. Cold, damp, poorly-ventilated and poorly-lighted houses are often associated with other unsanitary conditions which help to depress the physical condition of the occupants, and favor the development of diseases of which rheumatism is one. The social worker renders efficient service in helping to remedy the bad conditions of housing, ignorance as to proper diet, and neglect of cleanliness which are common among the poor of both large and small centers of population.

The effect of sudden changes of temperature is demonstrated in the frequency of rheumatism and other forms of acute arthritis among butchers and others whose work necessitates their entrance many times a day into cooling rooms. A change of occupation may be necessary in such cases to insure freedom from subsequent attacks.

Children, also adults, who are subject to rheumatism or are convalescent from an attack may be sent with benefit to a warmer climate during the inclement months of the year.

REMOVAL OF SOURCES OF INFECTION

A considerable proportion of cases of rheumatism are preceded by tonsillitis, and in recurrent forms of arthritis the tonsils are often chronically enlarged and infected, with enlargement of the lymph nodes of the neck. Removal of the tonsils has been followed in a considerable proportion of cases by cessation of attacks of arthritis. There seems to be no doubt that in some of these instances of successful prophylaxis by tonsillectomy the arthritis has resembled more closely the multiple arthritis of focal infection than that of typical rheumatic fever. In other instances tonsillectomy seems to have prevented the recurrence of undoubted rheumatic fever. It has already been pointed out, however, that while a series of typical cases of rheumatic fever resemble each other so closely as to leave no doubt of the propriety of regarding the disease as a clinical entity, there is frequently difficulty in determining whether in the individual case the disease is rheumatism or an arthritis due to another infection. There is much to recommend the theory that acute arthritis is caused by the invasion of joints by a number of possible invading organisms of varying degrees of invasive power in hosts of varying degrees of resistance, and that in a certain proportion of cases which go to make up the type recognized as rheumatic fever the invader is an

organism of relatively constant degree of invasive power, which leads to a fairly constant type of joint lesion.

Whether or not we concede that the tonsil may be the residence of the cause of rheumatism between attacks, and thus afford a portal of entry when for any reason the resistance of the patient is lowered, there is still another reason why attention to diseased tonsils is of benefit in preventing rheumatism. Persons who suffer from chronic tonsillar infection, whether children or adults, often show the effects of the chronic intoxication by evident disturbances of various functions of the body, apart from the development of definite metastatic lesions. When such persons are relieved of their infections, improvement of general health follows, and in so far as general good health and nutrition can assist in increasing resistance to disease, they are in a better position to withstand other infections. In this way, the removal of diseased tonsils, or other foci of infection, may have an additional prophylactic value in the treatment of rheumatism.

It has been urged that the present agitation in regard to the tonsil is a fad,—that many unnecessary tonsillectomies are being done, and that the removal of the tonsils often fails to prevent recurrences of rheumatism. It must be admitted that tonsillectomy, even when thoroughly performed, does not offer certainty of freedom from rheumatism, but experience has shown that when the tonsils are diseased their removal is advisable, unless there is some very clear contraindication.

Other possible local sources of infection, such as adenoids in children and the sinuses and teeth in older persons, should be sought for, and so far as possible should be removed. The need for these measures is more evident in the recurrent arthritis due to infections other than that of rheumatic fever, but the sufferer from rheumatism should also be allowed to profit by relief from chronic local lesions, which no doubt often contribute to the depression of his resistance to infection and make him more susceptible to the infection of rheumatism.

TREATMENT

The important objects in the treatment of rheumatism are the comfort of the patient and the prevention so far as possible of complications involving heart valves, both of which are best attained by prolonged rest in bed.

The sufferer from rheumatic fever has before him the prospect of a number of days or perhaps weeks of illness, during which in addition to the discomfort occasioned by fever and other symptoms of infection, he will suffer severe pain in many joints. It is well at the outset to recognize the possibility of a somewhat protracted illness and to arrange for details of the sick room which will add to his comfort, and prevent un-

necessary suffering. The sick room should be well ventilated, and if possible have an exposure which allows of the entrance of direct sunlight at some time during the day. The bed should be narrow, not more than three-quarter size, with firm springs and a smooth mattress. The usual type of bed is too low, and if the higher hospital type of bed is not available, blocks may be placed under the ordinary bed after removing the rollers. The use of a higher bed facilitates the frequent changes of the bedding and clothes of the patient, thus greatly lightening the labors of the nurse and lessening the suffering of the patient entailed by the necessary manipulations.

The bed covering, which should be light, should be prevented from making pressure on inflamed joints. Wooden barrel hoops cut in half, crossed, and wrapped with bandage, make very convenient supports. The use of blankets next to the patient is much less insisted on now than in former years. The prevention of chill following the sweats can be attained by frequent changes of sheets and gown, without undue disturbance of the patient if a competent nurse is in charge. The gown of the patient should be open at the back to allow of easy removal.

Treatment of Joints.—The rheumatic joint is the seat of an acute inflammation, excessively painful while it lasts, but likely to subside within a few days. While in part spontaneous, most of the pain results from motion, and immobilization of the affected joints affords a measure of relief to the patient often as great as that attained by analgesic drugs. Cotton wrapping surrounded by a bandage not too tight may be adequate, but more often the inclusion of a light, well-padded splint in the outer turns of the bandage is necessary to obtain immobilization sufficient to relieve pain. Cardboard is a familiar and easily obtainable splint material which often affords sufficient fixation to the smaller joints. The splint must be rigid enough to allow of the relaxation of involuntary muscular tension. Plaster of Paris casts have been sometimes advised, but the temporary character of the arthritis seems hardly to warrant the increased manipulations necessary in their application. The larger joints to which splints cannot be so readily applied may be immobilized with pillows or sand bags.

Pain in joints not relieved by immobilization may sometimes be relieved by hot compresses. In other cases cold applications are more grateful to the patient. The use of blisters and cautery is occasionally advised, but in general it would seem wiser to employ other measures, including analgesic drugs, before resorting to these remedies, which may leave the patient with an additional source of irritation to trouble him long after the arthritis has passed on to other joints.

Counterirritants such as liniments may be applied gently. When oil of wintergreen is not offensive to the patient it may be used, and, in so far as salicylates exercise a favorable effect on rheumatism, it serves a

double purpose in acting as a local counterirritant, and later, after absorption, on the disease itself.

Diet.—The appetite during the height of a severe attack of rheumatism is often very poor, so that it may be difficult to persuade the patient to take even small amounts of nourishment. It is important to meet the loss of energy entailed by prolonged fever, and to maintain nutrition in order to increase resistance to the infection. The lesson we have learned in recent years of the advantages of fuller diet in the treatment of typhoid might well be applied to the treatment of rheumatism, particularly as regards the giving of an increased amount of carbohydrates to meet the wastage entailed by prolonged high fever.

Milk is given freely unless distasteful to the patient, or one of the many milk products may be substituted. Cereals, including rice, bread, and gruels, will serve to raise the caloric value of the diet. Cream and butter and an occasional egg, or custard, may be allowed. A plentiful supply of fluids, which may include lemonade, fruit juices, and the alkaline mineral waters, should be given.

The diet should be increased upon convalescence, and may then include with benefit moderate amounts of meat.

It is important to avoid associating in the mind of the patient, particularly a child, the taking of medicine with the taking of food, and so far as possible the two should be given at different times. This is especially true in rheumatism where salicylates are likely to be given over long periods of time.

Drugs.—**SALICYLATES.**—The drug most widely used in the treatment of rheumatism is salicylic acid. The action of salicylic acid and its salts in rheumatic fever has been and still is a matter of controversy. On the one hand are those who believe that salicylic acid acts more efficiently in the arthritis of rheumatic fever than in other forms of arthritis and that its efficacy in relieving symptoms entitles it to be regarded as specific in the disease. Others maintain that its apparently specific effects are confined to the relief of pain, and that so far as a direct effect upon the infection itself goes, patients receiving salicylic acid require on the average as long a period for recovery as do those not so treated. The analgesic action of salicylates in arthritis is certainly not limited to that of rheumatic fever, for in cases of gonococcal arthritis, the lesions of which are in many respects similar to those of rheumatism, the relief of pain by salicylate is pronounced. Indeed salicylates are valuable in the relief of pain arising from a variety of causes. The arthritis of rheumatic fever is typically an evanescent process usually persisting in a joint for a few hours or days only, whether treated or not. When to the relief of pain following the use of salicylates there is added the disappearance of inflammation from the affected joints, the temptation is obviously great to attribute both results to the remedial agent. The weak point in the argu-

ment for specificity appears when new joints become involved while the patient is still receiving the same dose of salicylates that supposedly brought about the cure of the joints first involved. If we compare the effects of salicylates on other forms of arthritis with those on the arthritis of rheumatic fever, having in mind the distinction between symptomatic analgesic effects and those of a more specific nature, the results in the two classes of arthritis appear to differ for the most part only when the arthritis of nonrheumatic origin departs from the type of arthritis usually seen in rheumatic fever. Whether or not we accept the conception of rheumatic fever as an infection by the diplococcus rheumaticus, it is, however, a fact that the arthritis of rheumatic fever shows a remarkable uniformity in its course in the joints, and that the number of joints in which suppurative lesions or even permanent nonsuppurative changes occur is extremely small as compared with the arthritis caused by other organisms such as the gonococcus or streptococcus. In so far as the arthritis due to the latter is of slight degree and rapid in healing, such favorable outcome might be attributed to salicylates as well as in rheumatic fever, where evanescent lesions are more constantly seen. Clinical experience seems to indicate therefore that the favorable action of salicylates is attributable in large part to their analgesic action, and that the response to salicylates in a given joint lesion depends on the nature and severity of the lesion, which in turn is determined by the infecting organism and the general and local resistance of the patient. However, in view of the fact that the joint lesions in which relief of pain is accomplished by salicylates predominate in rheumatic fever and are less regularly seen in arthritis of other types, the action of salicylates in rheumatic fever may perhaps be thought of as "specific," though not in the same sense as the word is used in reference to the action of quinin against the malarial plasmodium, or of the arsenic compounds against spirochetes.

Sodium Salicylate.—The most commonly used preparation of salicylic acid is sodium salicylate. Opinions differ as to the optimal dose of sodium salicylate in rheumatism. Some advise large doses, approaching the toxic dose of 150 to 200 grains a day; others believe that much smaller doses are equally efficient. The middle course is probably advisable, allowing 60 to 90 grains per day during the first two or three days, or until the analgesic action of the drug is obtained. This dose would be attained by giving to an adult 10 to 15 grains every two or three hours for six doses during the waking hours. After two or three days, the dose is decreased to 10 grains four times a day. Unusual circumstances or individual susceptibility may require an increase or decrease of this dose. There is much individual variation in the degree of gastric disturbance occasioned by salicylates, some persons tolerating large doses without complaint, and others manifesting symptoms of gastric irritation, of burning in the epigastrium, and even pain after relatively small doses.

Sodium salicylate is preferably given in solution, well diluted with water, and not in capsules. Alkalies, such as sodium bicarbonate, should be given in at least twice the dose of the salicylate; they serve the double purpose of increasing gastric tolerance of the drug and of helping to maintain the alkalinity of the tissues. Milk or other suitable food taken just before the salicylate assists in preventing irritation of the stomach.

Delirium has been observed following large doses of salicylates, and minor symptoms such as tinnitus are seen even after smaller doses. While sodium salicylate alone can undoubtedly produce such symptoms, it seems probable that many of the complications, such as erythemas, and perhaps some of the instances of delirium have been caused by the disease, and not by the drug.

Other salts of salicylic acid, such as strontium salicylate, have been proposed as substitutes for sodium salicylate, but recent pharmacologic studies cast a doubt as to their superiority.

Derivatives of Salicylic Acid.—A number of compounds of salicylic acid have been produced which are said to be superior to sodium salicylate in that they produce less gastric irritation, or have a less disagreeable taste. The nausea and vomiting which occasionally follow their ingestion have been thought to be cerebral in origin.

Acetyl salicylic acid (aspirin) is widely used. It has the advantage of yielding the salicyl radical in large amount only in alkaline solution and hence passes through the acid stomach without being broken up to more than a slight degree. It should not be given in immediate company with alkalies. In small doses it may be administered in capsules, but when larger doses, 30 to 60 grains a day, are employed, it is preferably given in a powder.

Phenyl salicylate (salol) also is broken up only in alkaline solution, and is thus less irritating to the stomach than is sodium salicylate. Care must be used however in giving large doses over long periods on account of the possible toxic action of the phenol set free.

Among other salicyl derivatives of the acetyl salicylic acid type are diaspirin (succinyl disalicylic acid), diplosal (salicylo-salicylic acid), and novaspirin (methylene citryl salicylic acid). Corresponding to the methyl salicylate (oil of wintergreen) type are ethyl salicylate and mesotan (methyl oxymethyl salicylate) (New and Non-official Remedies, Amer. Med. Assoc., 1916). These and other synthetic products possess physical and chemical qualities in addition to their novelty which in special circumstances may recommend them in place of sodium salicylate and oil of wintergreen, but the action of the salicyl radical, for the sake of which they are for the most part given in rheumatism, is not different from the salicyl radical of sodium salicylate. When these products are given in doses containing equivalent amounts of salicylic acid, many experienced clinicians observe no constant advantage in their action as

regards lessened gastric irritation, over that of sodium salicylate when it is given with sufficient bicarbonate of soda.

ALKALIES.—Throughout the attack of rheumatism the patient should receive sufficient alkalies to prevent the development of acidosis. This may be accomplished by giving sodium bicarbonate and small doses of potassium bicarbonate or, combined with them, the salts of organic acids, such as the citrates. Sodium citrate may be administered in lemonade. Efficient alkalization is determined by the maintenance of an alkaline reaction in the urine.

The alkaline treatment recommended by some clinicians consists thus of thorough alkalization, and it is contended by some that cardiac complications are less frequent under this management than under treatment by salicylates.

OTHER ANALGESICS.—Antipyrin, acetanilid, and acetphenetidin (phenacetin) may be cautiously given when pain is not well controlled by salicylates.

They are best given in 3 to 5 grain doses, every 3 or 4 hours, but must not be too long continued. Caffein may be combined with them to combat their depressive action. In cases of extreme restlessness or insomnia due to pain it may be advisable to give morphin, gr. $\frac{1}{8}$ -gr. $\frac{1}{4}$, or codein, gr. $\frac{1}{4}$ -gr. $\frac{1}{2}$, hypodermically, rather than to temporize with less efficient drugs.

VACCINES AND SERA

The treatment of rheumatism by antistreptococcic sera and by the subcutaneous injection of vaccines has not yielded results which warrant a recommendation of the method. The intravenous injection of non-specific bacterial or other protein, with its resulting chill, rise in fever with subsequent fall, and coincident symptoms of shock, does not appear to be justified by the average clinical results which follow the treatment.

Our ideas concerning the mechanism of the development of immunity are undergoing rapid changes and it seems probable that in addition to changes in fluids and cells which appear to be specifically related to the invading organism, other more general and less specific alterations in body fluids and ferments may take part in the struggle of the body against the disease producing organism. Until the nature and methods of control of these nonspecific processes are better understood, it seems wise to restrict the use of nonspecific proteins believed to assist in their mobilization, especially in view of the fact that clinically the results obtained do not convince one as to their practical value.

COMPLICATIONS

Hyperpyrexia.—Sudden and alarming increase of fever, with accompanying delirium, is occasionally met with, and has been called "cerebral

rheumatism." Cold baths and packs aid in allaying restlessness and in reducing the temperature.

Cardiac Lesions.—The most serious and frequent complications of rheumatism are those involving the heart, and they may occur in spite of all efforts to prevent them. The involvement of the myocardium as well as of the endocardium and pericardium has led to the use of the appropriate term "the carditis of rheumatism." The most important prophylactic against cardiac complications is absolute rest in bed, and whenever there is suspicion of cardiac involvement, the period of rest in bed should be prolonged a number of weeks after the subsidence of the acute rheumatic symptoms. Any increase of fever or increased rate or irritability of the heart occurring during the attack should direct special attention to the heart. A precordial murmur may develop coincidentally with the anemia without valvular disease, but all murmurs are to be carefully observed. Daily examination of the heart will prevent the physician from overlooking both valvular and pericardial disease, the finding of which may explain many otherwise puzzling symptoms.

The ice-bag and ice-coil applied over the precordium are extremely valuable in combating both the irritability of the heart and the pain of pericarditis. Counterirritation in the form of mustard plasters or fly blisters along the sternum have been advised. When extensive pericardial effusion occurs, the heart action may be greatly embarrassed and in extreme cases paracentesis of the pericardium may be advisable. The administration of sodium cacodylate in doses of 3 to 10 grains daily by deep hypodermic or intramuscular injection has been followed by rapid subsidence of effusions, both pericardial and pleural, in rheumatism. The improvement has seemed to some observers so rapid as to suggest a specific action of the drug in cases of this sort; others argue that pericardial and pleural effusions frequently subside spontaneously, and that the improvement noted is not necessarily a result of drug therapy.

Symptoms of serious cardiac embarrassment call for a careful examination to determine their cause. A rapidly developing pleural effusion, which may seriously interfere with heart action, calls for paracentesis. Care must be taken to distinguish left pleural effusions from large pericardial effusions.

Cardiac insufficiency, whether muscular or valvular in origin, may require cardiac stimulants to tide the heart over the emergency. In such cases, the heart is to be treated as in incompetence arising from other causes. Digitalis is of great assistance, but should be withdrawn as soon as is consistent with safety.

Anemia.—Anemia in rheumatism is frequent and often of high grade. As soon as the acute attack subsides, iron is indicated. Iron in the form of Bland's mass, or the citrate of iron, combined with a full diet, including vegetables and meat, is usually sufficient to insure a rapid return

or the blood to normal. Arsenic, gr. 1/100, is sometimes combined with the iron, or given as Fowler's solution, m. ii to x. The prolonged persistence of anemia following an attack of rheumatism suggests the persistence of the original infection, or the possibility of some lingering local infection, as in tonsils or sinuses, or occasionally the development of ulcerative endocarditis.

CHAPTER XVIII

ACUTE BACILLARY DYSENTERY

CHARLES WARREN DUVAL AND ISAAC IVAN LEHMAN

326. Line 12 *read*:

broken doses of 1-6 gr. **to** 1-4 **gr.** (0.01 gm. to 0.015 gm.) every half hour

327. Lines 23-25 *read*:

For collapse in the acute stage stimulants, such as camphor **and** alcohol, are to be used. Hypodermoclysis of normal salt solution is invaluable.

CHAPTER XIX

ANTHRAX

WILLIAM H. PARK

331. Line 26 *add* after "year." :

The vaccines must be very carefully standardized so as to be both effective and not dangerous.

332. Line 5 *read* :

In the production of the serum the **most uniformly good** results have been obtained

Line 17 *add* after "injection." :

Horses differ greatly in the potency of the serum which they produce so that several should be injected and the best chosen.

Line 35 *add* after "kind." :

Several severe cases occurring in the vicinity of New York City in the fall of 1915 were treated with serum without evidence of benefit.

CHAPTER XX

HYDROPHOBIA

WILLIAM H. PARK

336. Line 8 *read*:

Department, **by Cabot.** The cauterization was done twenty-four hours after the

Line 17 *read*:

Last year Poor repeated the experiment under conditions simu-

343. Line 6 *read*:

mended. **Quinin in large doses has been given. There is no evidence that it is a curative treatment.**

Line 13 *add* after "saliva.":

The preventive Pasteur treatment is given in the article by Dr. A. W. Williams, Vol. V, page 725.

CHAPTER XXI

TETANUS

WILLIAM H. PARK

351. Line 28 *add* after "given."

The use of the intraspinal in connection with an intravenous injection has displaced all other methods and is described under the serum treatment of tetanus. Several cases are reported at the end of this series.

352. Lines 12-15 *read*:

10,000 units, and should have been given **one-half** intravenously and **one-half** intraspinally. **A second injection 24 hours later would have sufficed.** The immediate **giving of the** intravenous and intraspinal doses is the most important point to be insisted on.

353. Lines 32-33 *read*:

am inclined to think this dosage too large. A large dose of antitoxin, **given intraspinally**, might have been of use in this case.

355. Line 33 to **356.** Line 6 *substitute*:

Case 6.—F. D., girl, aged 10 years, seen in consultation with Drs. W. B. Anderton and A. A. Smith, fell, striking her forehead on the ground, receiving a lacerated wound three-quarters inch long over one brow. This was properly disinfected and sutured, healing promptly. Seven days later there was a facial paralysis on the side on which the wound was received. Thirty-six hours later, the jaws were firmly locked. Eight hours after this symptom was noted, the patient received 3,000 units of antitoxin intraspinally and 10,000 intravenously. Several subcutaneous injections were later given. The tetanic spasms were largely confined to the muscles of the jaw and pharynx, and later, the abdominal muscles; attempts at swallowing and the slightest external irritation caused contractions of the muscles of the throat and larynx, cyanosis, general convulsions and unconsciousness. Such convulsions occurred on fifty or more occasions, together with innumerable minor spasms. Pneumonia developed later, resolution being very long delayed. After a pro-

tracted convalescence and extreme emaciation, the patient made a perfect recovery.

Case 7.—Thomas B., laborer, was admitted April 1, 1914, to the New York Hospital, with multiple lacerations of scalp and traumatic amputation of toes of the right foot. The wounds were immediately disinfected with iodine and irrigated with iodine solution. The following day, amputation of the toes was performed. April 10 (incubation nine days), there was slight stiffness of the jaws, which was not reported until the following morning. April 11, 1,500 units of antitoxin were given in the tissues about the wound and 3,500 intravenously; later on the same day, 3,000 units into the tissues about the wound and the same amount intravenously. April 12, the patient was very much worse, and was given 13,000 units intravenously, 8,000 intraneurally and 7,000 into the tissues about the wound. April 13, his condition was still more unfavorable. There was marked opisthotonos. Eight thousand units of antitoxin were given into the spinal canal and 9,000 intravenously. Following the intraspinal injection the temperature rose to 105° ; there were severe headache, convulsions and semicoma. April 14, the patient was comatose throughout the day. April 15, the patient was conscious, and there was less rigidity. April 16, there was much less rigidity; and the patient swallowed fairly well for the first time. The patient continued to improve and was discharged cured, April 30.

Comment.—Through a series of misunderstandings, this patient received still further intravenous injections of antitoxin following the intraspinal dosage, although an examination of his blood showed a tremendous antitoxic content. How much credit should be given the single intraspinal dose for the recovery in this case it is difficult to say. It is to be noted, however, that the first real improvement followed shortly after its administration.

CHAPTER XXII

GLANDERS

WILLIAM H. PARK

358. Line 27 *read*:

action produced. It is well to begin with injections of **ten** millions,

Line 29 *add* after "produced.":

The reaction from the injections is similar to that produced by mallein. If a larger dose than the one advised is given, a too severe reaction may occur due to sensitization.

CHAPTER XXIV

THE GENERAL AND SPECIAL TREATMENT OF SYPHILIS

WILLIAM S. GOTTHEIL

397. Line 16 to **404.** Line 11 *substitute*:

c. Salicylate of Mercury.—This is the salt that I habitually employ; it is as efficacious as calomel, is better borne and less liable to cause accidents, and its suspension is readily made and keeps indefinitely. It is therefore well suited for the general practitioner, who does not treat syphilis patients every day. The technic of its preparation and administration is important; and this, together with general directions and considerations of objections to its use, will be considered in some detail.

1. The Injection Fluid.—The insoluble basic salicylate of mercury, containing 59.52 per cent. of metallic mercury, and not the soluble neutral salicylate, is to be employed. Watery fluids, glycerin or gum, or organic oils, are not suitable menstrua; they are unstable and variable. A mineral petroleum oil, of a specific gravity sufficient to keep the salt in suspension for a reasonable time, and yet not too thick to flow through the needle, is required; and the ordinary liquid petroleum commercially known as albolene is the product that I have found most suitable for the purpose.

The suspension must be carefully and slowly made, since thorough comminution makes a more perfect emulsion, one less liable to cake on long standing, less apt to clog the needle, and less painful to the patient. It can be prepared, however, in larger quantities, and it keeps indefinitely. The powder should be thoroughly rubbed up in a mortar, the oil being added a few drops at a time. This process should take an hour at least. Many of the emulsions that have been sent to me with complaints have been imperfectly prepared; the sediment has been coarsely granular and flaky, and has caked quickly into masses that could with difficulty be reemulsified; so that the needle readily became clogged, the patient suffered unnecessary pain, and the entire method was brought into disrepute.

It is a minor but important convenience to have the emulsion put up

in the ordinary half-ounce phials, and not in any larger or salt-mouthed bottle. The mouth of these phials fits the end of the ordinary hypodermic or that of the special syringe to be described later. The emulsion can be drawn into the syringe after shaking up the fluid by inverting the instrument and bottle, thus avoiding exposure and the risk of contamination of the injection fluid. A half-ounce bottle suffices for from 25 to 50 injections; so that whatever the cost of the preparation, the treatment is entirely inexpensive.

The emulsion and containers are now subjected to one thorough and careful sterilization; and rather for the purpose of rendering the containers safe than for treating the emulsion itself, for both the mineral oil and the salicylate are unchangeable and not liable to microbic contamination.

The new bottles and corks are boiled and permitted to drain dry; each bottle is then entirely filled with emulsion and stoppered with a pledget of sterile cotton. They are then stood up in a water bath filled with cold water up to their necks; and the bath is then gradually brought to a slow boil and kept at it for one hour. The cotton pledgets are replaced by the sterilized corks, which are tied to the necks of the bottles and sealed with melted paraffin.

These filled bottles keep indefinitely and are ready for use at any time. Sterilization at the time of employment is unnecessary. I habitually keep several bottles of different strengths in use at one and the same time and use them up to the last drop, though it may take a long time. For experimental purposes I have left specimens uncorked for months; the emulsion has remained sterile, though there was a layer of dust and microbes on its surface.

Attempts to put up the emulsion in sealed ampules, each containing an average dose, have been failures. The comminution is not fine enough, and the amount is so small that it cannot be shaken up properly; so that an irremovable deposit remains in the ampule, and the dosage administered is uncertain. Besides this, the method is rendered unnecessarily expensive.

Not only is the suspension thus prepared absolutely stable; it does not affect metallic surfaces, and even has a distinctly preservative action on them. So that I do not cleanse the suspension from the syringe after using it; the fluid is sterile and unchangeable, and forms the best possible lubricant and preservative for the syringe. My syringe has a solid metal plunger; and in the oldest one, which has seen at least five years of service, and whose inside has never been cleansed of emulsion, even the polish of the end of the plunger has not been dimmed by constant contact with it. The plating of the sides of the cylindrical piston is worn from friction of the cap washer; but otherwise the metal parts are perfectly preserved in the oil. An additional advantage in not cleansing

the emulsion out of the syringe is that it leaves whatever space there may be in the interior of the instrument filled with sterile oil.

In the endeavor to reduce the size of the injection mass and so minimize the mechanical injury inflicted on the tissues by the injection, I have experimented largely with suspensions of the salicylate stronger than the 10 per cent. one employed at first. A 50 per cent. emulsion can be made; it forms a thick, creamy fluid, which does not cake even on long standing, and can be readily shaken up. The dose is so small, 2 to 5 drops, that tissue injury and pain are very slight; but the amount of solid matter in the emulsion is so great that considerable technical skill is required for the injection; the needle is very apt to become clogged during the injection, and the entire apparatus must be cleansed after use. A 20 per cent. suspension is not open to these objections, and is the one that I now habitually employ and recommend. The ordinary dose is from 5 to 10 drops.

2. The Injection Implement.—Any syringe can be used—provided that it permits of accurate drop dosage, and that its barrel is of glass, so that the condition of the fluid as to air bubbles can be observed—and any needle, provided it is long enough to reach the muscle mass and large enough in caliber not to be plugged by the emulsion. The needle-syringe joint must be of the slip or bayonet variety, for ready detachment, as will be seen below. Of course the ordinary hypodermic used for watery solutions must be entirely dry before using the emulsion in it; and it must be carefully cleansed afterwards.

Some years ago I devised a syringe for these injections which fills these requirements and has several additional advantages. The barrel is of accurately calibrated thermometer glass, graduated in drops, and so narrow in diameter, though the glass is thick, that each drop measures three-sixteenths of an inch. Air bubbles can be seen and expelled, and accurate dosage is ensured. The piston is a solid metal rod, fitting the lumen of the tube accurately; there are no washers save one under the cap, so that only glass and metal come in contact with the suspension. The piston head is a large, heavy, flat disk, giving weight to the instrument for the rapid insertion plunge and permitting it, when filled, to be placed upright beyond reach of contamination. The needle end is a slip joint, permitting instantaneous detachment; it fits accurately into the needle cap; the piston fills the syringe barrel accurately; so that, except the minute column of fluid in the needle head of the syringe, there is no vacant space at all when the piston is driven home. A small pair of arms on the head facilitates handling.

The needles should be at least $1\frac{1}{2}$ inches long, so as to reach the muscle; deposition of the injection in the subcutis is painful, and leads to imperfect absorption and persistent nodules. Females require an especially long needle; and two two-inch ones, as well as four shorter ones,

come with each syringe. The caliber of the needles called "antitoxin" is about right; smaller sizes are apt to cause trouble.

Special sterilization of the syringe and needle is not only unnecessary; it quickly ruins the instrument. Boiling is especially deleterious; it destroys the calibration on the barrel and loosens the cement that holds its ends; and it is very wasteful of needles. The closed syringe contains no air; the very small amount of vacant space is filled with the sterile and metal-preserving emulsion. The same is true of the needle itself. The outside of both is glass and highly polished metal; and only those parts of the instrument that penetrate or come in contact with the tissues need give us concern. Passing the slip-joint end of the syringe once or twice through the Bunsen or spirit-lamp flame sterilizes it absolutely. Passing of the needle with the stylet in it through the flame is sufficient also. The inside of its lumen is not exposed to contagion, and is moreover coated with the sterile oil; and the intense heat of the flame is entirely sufficient to destroy any contagious organisms that may have lodged there. Needle flaming should be done with fair rapidity; for if it is too prolonged the temper is taken out of the instrument. I regard this as rather an advantage, provided the point is kept sharp enough for easy penetration into the skin. If any obstacle is encountered the needle bends instead of breaking off. This may be bad for the needle, but it is advantageous for both patient and operator.

3. The Injection Site.—Only the gluteal muscles have a muscle mass large enough and a skin insensitive enough to be eligible sites for the injections, which must always be deeply intramuscular, and never subcutaneous or subfascial. Even the large muscles between the shoulder blades are ineligible, since the patients complain of pain when lying in bed and when using their arms if these are employed. The region between the trochanteric fossae and the middle line of each side, an area of at least four by six inches, gives us six separate sites at different levels. By systematically using and noting the sites employed in successive injections it is at least six weeks before the same area is used again. Reaching the buttock mass from the side is bad; and employing the trochanteric area, as is not infrequently done, is to put the injection in or under dense connective tissue layers and cause needless pain and disability. With the patient standing upright in front of the operator, the position to be preferred in making the injection, the direction of the needle should be downward and outward, so as to reach the center of the muscle mass.

The skin of the injection site can be cleansed in any of the ways ordinarily employed. The plan that I have used for years is rapid and perfectly satisfactory. It is scrubbed with a piece of gauze and a watery lysol or phenol solution, and then the process is repeated with plenty of ordinary ether. Superficial detritus and fatty matter are thus removed;

and the transitory cold that is produced perceptibly diminishes the pain of the puncture.

4. The Injection.—With the patient standing upright, back to the operator and heels together, he cannot see what the latter is doing or interfere with his work; the recumbent position is neither necessary nor useful. An important point is to have everything ready beforehand, and to be as rapid as possible in the manipulations. Quickly done, and with the skin well etherized, the injection can often be given without the patient feeling it at all.

The needle with its stylet in place is flamed; for it may be necessary, as will be seen later, to use the latter. They are then placed in a safe location; the needle end of the syringe is then flamed, and the instrument stood up on its head. The emulsion having been thoroughly shaken up, the syringe is filled with a little more than will be needed by inverting the bottle with the syringe in the place of the cork, and withdrawing the piston. The filled instrument is then stood on end again, to permit air bubbles to rise to the top. The injection site is prepared as above directed and covered with a pledget of sterile gauze, which the patient holds in place. All air bubbles are then expelled from the syringe, the gauze pledget is removed from the injection site, and the instrument is plunged rapidly and up to the hilt in the place selected.

The needle being *in situ*, a certain precaution must always be observed. Practically the only danger of the injection is that of fat embolism of the pulmonary vessels, though its importance is greatly overestimated. If the opening of the needle is in the lumen of a vein the oily emulsion will be injected directly into the circulation. This danger can be avoided with certainty by detaching the syringe from the needle immediately after the insertion of the instrument and watching the emulsion-filled needle cap for a few seconds. It is filled with a concave white dome of emulsion, due to the capillary attraction of its walls. The least flattening of this dome, the least tendency to inversion of the concave emulsion cap, shows that the opening of the needle is in a place where there is pressure from behind, and that can only be a vessel. It is bad practice to regard only the actual expulsion of the injection from the unattached needle, or to wait for an actual outflow of blood before deciding that the site is dangerous; venous pressure is slight, and in a small vessel may not be sufficient to do either. If the site is not perfectly satisfactory the needle must be withdrawn, the puncture sealed with plaster, the needle resterilized, and a new injection site employed. Reaching the interior of a vessel happens only in very few cases; certainly not more than once in some scores of punctures. On the other hand, it has happened to me a few times to strike a vessel at the second puncture, and to have to make a third one. Piercing a vessel with the needle in its course through the tissues is of no consequence; the opening in the vessel is plugged with

the needle shaft while the injection is in progress; and the minute vascular lesions do not permit any of the fluid to reach the veins after the instrument is withdrawn. Oozing of blood from the puncture after the injection is therefore of no consequence at all; a little pressure with a pledget of gauze and a piece of plaster is all that is required for it.

When the needle is implanted in a safe site the syringe is reapplied; and it is this necessity of removing and reapplying the syringe after the needle is inserted that makes a slip or bayonet needle joint so advisable. An ordinary screw joint takes longer to manipulate; and the needle point is very liable to be displaced after the injection site has been judged safe. The injection itself is then made rather slowly and steadily. When it is completed the syringe and needle are withdrawn as quickly as they were inserted; and here, as before, rapidity of execution will do much for the patient's comfort. Immediately on withdrawal the orifice in the skin is closed with a pledget of cotton, and a small piece of zinc oxid adhesive plaster is applied; this need not remain on more than an hour or so. I do not massage the injection site after the operation. It does no especial good; and, theoretically, it might force some of the emulsion into a vessel that has been wounded by the needle passage.

The immediate effects of the injection vary with the sensitiveness of the patient and the skill of the operator; in most cases it is practically painless. A few hours afterwards there is a bruised feeling in the part; to use the patient's own expression, he feels as if he had been kicked. This wears off in a few days, as does also the slight discomfort when sitting down. Hard persistent indurations are rare, though there is a good deal of difference between the rapidity of absorption of the injected material in different cases. When they do persist either the emulsion has not been prepared with sufficient care, so that the salicylate is deposited in comparatively large and irritant masses in the tissues, or, what is more commonly the case, the puncture direction has been wrong, or the needle has been too short—in either event leading to the deposition of emulsion in the subcutaneous fatty tissue where vascularization is poor and absorption slow, or putting it under some resistant fascia. Once formed, these tender indurations may last for some time, but they do no other harm; they are slowly absorbed and finally disappear. It must not be forgotten, also, that with every injection a certain very small amount of muscle tissue is necessarily compromised, and is replaced by connective tissue. In giving long or repeated series of injections care must be taken not to strike exactly the same spot that was used before. The difference between the soft muscle and the hard scar tissue can be felt at once with the needle point; and any attempt to force the injection out at that point will cause needless pain and slow absorption of the injection fluid.

The needle may become plugged with the salicylate during the course

of the injection; this is especially liable to happen, of course, with the stronger emulsions; and this is why I do not recommend the 50 per cent. suspension for general use. It practically never happens with the 10 per cent. suspension, and very rarely indeed with the 20 per cent. one. When it does occur the syringe must be detached from the needle and the sterilized stylet used to push the occluding mass forward; it is hardly ever necessary to suspend the injection and puncture at another site.

There is probably always a systemic reaction of some kind after the injection; but it is usually so slight as to pass unnoticed. Chilliness and flushes, slight headache and malaise, or a general feeling of discomfort, may last for a number of hours. Once in a while there is a distinct febrile reaction. Such effects are to be expected after the injection of a foreign body of this nature; but I have never found them severe enough to interfere with the treatment. The great majority of patients do not complain of the aftereffects of the injections at all.

5. Objections to the Mercury Salicylate Injections.—Various criticisms, mostly groundless, often due to inexperience and faulty technique, and a very few with some basis, have been made of the method. It has been claimed that the injections are very painful, that they leave persistent inflammatory nodules behind, that infections occur, and that there are dangers from embolism, general mercurial intoxication, and local gangrene and sloughing. There has never been any question of their remarkable therapeutic efficacy.

There is necessarily some slight *pain* connected with the puncture; but this, as explained above, is almost entirely governed by the care exercised in making it. It is positively trivial in the insensitive gluteal skin if that is thoroughly cold from the ether, if the needle is sharp, and if insertion and withdrawal are made with celerity. Delicate women stand it without complaint, especially when they do not see the operation. Of course there are individuals, even of the male sex, who faint when an acne pustule is opened; and once in a long time I meet a patient who says that he cannot stand the injections.

The later discomfort is a different matter; it varies greatly, though there is a little in all cases. In most patients it is merely a very bearable soreness of the glutei, not enough to interfere with their occupations. The larger the muscle mass and the thicker the fat cushion over it, the less the discomfort; hence women suffer less than men, and fat less than thin individuals. The discomfort reaches its height by the second day, and is usually gone by the fourth.

As explained above, some injury is necessarily done to the muscular tissue; the inflammatory action set up, however, soon passes off; and the small connective tissue induration occasioned disappears, so that in a few days or a week or two nothing can be felt of it.

Infections can and should be avoided; I have encountered them two

or three times, but always under conditions where a proper technique could not be carried out. The abscess, if large, must be opened and drained; if small, it will be absorbed without trouble.

Fat embolism of the lungs can be avoided if the injection is given *secundem artem*. If it does occur the symptoms are usually slight and soon disappear. In some cases, however, they may be alarming to those who have not encountered them before. There may be sudden pain in the side and pain on respiration; there may be violent fits of coughing and blood-stained expectoration. But these symptoms invariably disappear in a few hours; for the amount of fatty material injected is so small that the tissues are quite able to take care of it. The essential innocuousness of the occurrence is well recognized. I am informed that in a certain very popular genito-urinary clinic in New York, where the injections are given with few precautions, embolism occurs quite frequently and but little attention is paid to it. I myself, in many thousands of these injections, have never encountered it; and my assistants in various hospitals and dispensaries, where the technique is not as careful as in the office, have seen but very few instances of its occurrence.

The cases of *gangrene and sloughing* after the injections date from the time when the method was new and unfamiliar and the technique imperfect. Those who dwell on its occurrence have gotten their facts from old records rather than from experience. I have never met with a single case of the kind.

As to *general intoxication* from the drug, no one can claim that the administration of mercury in any form and by any method is a perfectly indifferent procedure. The drug is a poison, and idiosyncrasy to it occurs, though with extreme rarity, especially among the spirochetes infected. It may be desirable, in a patient who has never had mercury, and whose individual attitude to the drug is still unknown, to begin with a small initial dose, giving the full amount a few days later; I do not do so, any more than I would when giving mercury by the mouth. Intoxication may occur with this as with any other method of medication; but with this as with all other modes of administration a little care and observation will enable us to avoid it.

One criticism has apparent cogency; it is claimed that, the dose of the insoluble preparation once injected, the physician loses all control of it; the mercury will continue to be absorbed as it becomes changed into a soluble compound. The same objection is valid for other forms of administration; and the measures to relieve it are just as efficacious. I have never yet had occasion to resort to excision of the mercurial focus.

437. Line 13 *add* after "only.":

THE TREATMENT OF SYPHILIS WITH SALVARSAN AND MERCURY

DAVID GEIRINGER

Since the year 1903 considerable changes have taken place in our knowledge and treatment of syphilis. In that year Metchnikoff by transmitting the disease to apes placed it among the infectious diseases. In 1905 Schaudinn discovered the specific spirochete and shortly afterward in 1906 Wassermann gave us a method of serum diagnosis. In 1910 Ehrlich, who had been working along therapeutic lines, had prepared an arsenical compound possessing active antisyphilitic properties which he called salvarsan, "606." These important diagnostic and therapeutic aids opened the way for work along modern lines.

Although arsenic had been used for a long time in the treatment of syphilis, it could not be given in sufficiently large doses to produce any profound therapeutic effect because of its toxic properties. Various synthetic products were used with but indifferent success, for example, arsenious acid, sodium cacodylate, atoxyl, soamin and arsacetin. It remained for Ehrlich to prepare an arsenical compound which could be given in large enough doses to have an active antisyphilitic action without producing the toxic symptoms heretofore obtained. Although his hope of "therapia magna sterilisans" has not been realized, it has already been sufficiently demonstrated that salvarsan and its derivative neosalvarsan are the most powerful antisyphilitic agents that we possess at present. If used in sufficient dosage in combination with mercury and iodine, the disease is more quickly brought under control and the time required for cure materially shortened.

The specific action of salvarsan depends upon whether or not it can reach the spirochetes. If they are accessible, they will be destroyed and a cure result. If they are deeply seated in the tissues away from the direct influence of the drug, they will survive and under favorable conditions multiply and cause relapses.

SALVARSAN

Salvarsan, "606" (dioxydiamido-arsenobenzene dihydrochlorid), is a yellow crystalline hygroscopic powder, very unstable when exposed to air. It is very soluble in water, yielding a solution strongly acid in reaction. It contains 31.57 per cent. arsenic. It is administered by the intravenous and intramuscular routes.

Intravenous Administration of Salvarsan.—Formerly when salvarsan was administered intravenously the apparatus employed was complicated

and cumbersome. It consisted of one or two irrigating cylinders with long lengths of rubber tubing. Special needles of various sizes and shapes were recommended. Large amounts of water, ranging from 250 to 300 c.c., were employed for dilution. Special attention was directed to the temperature of the water, and different amounts of sodium chlorid were advised to make the resulting solution isotonic. With all these precautions, severe reactions were nearly always the rule. It was believed that they were caused by the large dose of arsenic suddenly thrown into the circulation. Wechsellmann soon after demonstrated that the reactions were due to the dead bodies of bacteria and fungi, or their toxins, which quickly contaminated distilled water that had been allowed to stand. As a result these disagreeable after-effects are almost entirely eliminated by the use of freshly distilled water in preparing the solution. Further experience also taught us that the large amount of water originally employed contributed also to the reaction. Observers differ as to the amount of water for dilution. The quantity advised varies from 35 to 250 c.c. for 0.6 gram salvarsan; 150 c.c. is most frequently used. Personally I find 15 c.c. for each decigram of salvarsan most satisfactory. If the drug is administered in greater concentration, disagreeable and even alarming symptoms may occur while the patient is still on the table. Several years ago, at the Post-Graduate clinic, following the technique employed in the Dreyfus clinic at Frankfurt, I used only 35 c.c. for 0.6 gram salvarsan. In a series of 25 cases we met with some very intense reactions during and immediately following the injection. Marked suffusion of the sclera, feebleness and rapidity of pulse were not infrequent. Nausea with vomiting and violent retching occurred in several instances. Two cases had chills followed by epileptiform convulsions, one patient suffering from incontinence of urine. The dose of the drugs ranged from 0.4 to 0.6 gram. As these were selected cases and we were careful in our technique, we attributed these reactions to the concentration of the drug, especially in view of the fact that most of this series had previously experienced no such reactions when less concentrated solutions were used. We then started with the higher dilutions and gradually diminished the amount, finally deciding upon 15 c.c. for each decigram of the drug. The immediate reaction is rarely more than a throbbing in the head or a bad taste in the mouth and the after reactions are absent or mild. The use of saline in preparing the solution may be omitted. It complicates the procedure, and I have discontinued it without any apparent disadvantage. I employ only freshly distilled water at a temperature ranging from 100 to 105° F.

There are a number of small portable stills now on the market which will distill the required amount of water in from 15 to 20 minutes. The water can thus be freshly prepared just before use, thereby eliminating the so-called "water error" described by Wechsellmann.

EQUIPMENT REQUIRED

Hand syringe, capacity 100 c.c., Record or Luer type.

Pointed needle, one inch long, gauge 16 to 18.

Rubber catheter tubing, three inches long, 12 to 14 Fr., to connect the needle with the syringe.

Graduated wide-necked glass jar, capacity 8 ounces.

A 2 c.c. graduated pipette.

Glass funnel and sterile gauze for filtering.

Sol. sodium hydrate, 15 per cent. chemically pure.

STERILIZATION.—The apparatus is sterilized by boiling. The ampule of salvarsan is placed in 95 per cent. alcohol and dried with sterile gauze.

PREPARATION OF PATIENT.—A saline cathartic is administered in the morning. The meal preceding the injection should always be light.

The site of the injection is preferably the flexure of the elbow. Occasionally in stout subjects or in women with very small superficial veins I have succeeded in finding larger vessels over the instep or on the inner side of the ankle. A tourniquet applied above the elbow makes the vessels more prominent. If the veins cannot be seen they should be felt for and their course marked out with a blue pencil. The integument is sterilized by painting with iodine. If the veins are small, have both arms prepared.

PREPARATION OF THE SALVARSAN SOLUTION.—1. Place the necessary amount of freshly distilled water in sterile wide-necked bottle. Use 15 c.c. for each decigram of salvarsan.

2. Add required dose of salvarsan.

3. Shake vigorously until the salvarsan is completely dissolved. The solution must be clear and contain no gelatinous particles.

4. Add necessary amount of sodium hydrate with pipette as described in circular accompanying the ampule. The addition of soda at first causes the solution to become turbid. It usually promptly clears up on shaking. If it remains cloudy add more soda, drop by drop, shaking each time until the solution becomes clear. If necessary, filter before using.

5. Draw up solution into the syringe and expel any air bubbles.

TECHNIQUE.—*Syringe Method.*—Having located a good-sized vein, steady it between the thumb and forefinger of the left hand. Insert the needle through the skin and pass it through the subcutaneous tissues for about $\frac{1}{4}$ inch in the same direction as the vein. The handle end of the needle is then given a slight upward tilt, which causes its point to impinge against the wall of the vein. Slowly push the needle through the vein. As the needle passes through the wall a slight resistance is felt, which ceases as soon as its lumen is entered. If the puncture has been properly performed, blood will flow freely. Steady the needle with the

left hand and loosen tourniquet. Connect the syringe with the needle by means of small piece of catheter tubing. The injection is then slowly made. If the vein has been properly entered there will be a free flow of the solution without causing any swelling or pain at the site of injection. If an increasing swelling is noted or pain and burning complained of, the needle is withdrawn, flushed out and inserted in a different vessel. The swelling and pain indicate that some or all of the solution is being injected into the subcutaneous tissues. If the injection is persisted in when this occurs, a badly swollen and very painful arm will result, leaving dense persisting indurations and disfiguring scar formation. This possibility should always be avoided because it renders the arm useless for further injections on account of the persisting tissue infiltration, to say nothing of the pain and suffering needlessly produced.

In a few cases it sometimes happens that, although the injection has been properly performed, 5 or 6 days later the injected vein feels thickened, cordlike and sensitive to pressure. This is in all probability a localized phlebitis. It rarely requires any attention, usually subsiding in a week or two. It is of practical importance, in that no attempt should be made to repeat the injection in the affected area, as failure will result due either to partial or complete obliteration of the lumen of the vein. A case has been reported in which death occurred, due to cerebral embolism. The surgeon mistook the thickened vein for a distended vessel, began the injection and evidently dislodged a thrombus, causing sudden death.

Usually there is no difficulty in entering the vein. The surgeon should bear in mind that even in stout subjects the veins lie just beneath the skin, separated from it by a thin layer of loose connective tissue. In subjects who follow sedentary occupations and in females the superficial vessels are very small and are entered with great difficulty. In such a pointed needle of very fine caliber should be used. If after several attempts failure results, it is best to go to the other side, incise the skin over the vessel, after which the injection is made in the same way that a saline infusion was formerly given.

Gravity Method.—Some still employ the gravity method. The apparatus consists of a graduated cylinder holding about 300 c.c. To it is attached four feet of rubber tubing. The cylinder is suspended three feet above the patient's head. The salvarsan solution is poured into the cylinder and any air bubbles expelled. The needle is then inserted into the vein, after which it is connected with the cylinder by means of a coupling on the end of the tubing. In comparison with the syringe method the gravity apparatus will be found cumbersome and harder to manage, for which reasons I have long discarded it.

When the injection is completed the needle is withdrawn and the puncture wound sealed with collodion.

AFTERTREATMENT.—The patient is left lying upon the table for 15 minutes, after which he is allowed to go home with instructions to spend the rest of the day quietly, and not to indulge in rich or greasy food. When the subject is in good physical condition I have no hesitation in administering the injection in the office or clinic and allowing him to go home immediately afterward. In weak, poorly nourished individuals, or in cardiac and nervous syphilis, the injection should be given in bed and the patient kept in bed until the next morning.

Occasionally while the solution is being injected certain symptoms may occur which might prove alarming to the beginner. The patient's eyes may become suffused, his face becomes flushed or he may complain of throbbing in the ears or of a bad taste or smell. These symptoms always disappear in a few moments and should not cause the surgeon to stop the injection. If, however, the patient manifests extreme distress or apprehension or the pulse becomes slow and feeble and dyspnea occurs, the injection is discontinued. The inhalation of aromatic spirits of ammonia has always dispelled these alarming symptoms very promptly.

Some authors compare these immediate reactions to anaphylaxis and describe them as occurring after several injections have been given. This has not been my experience. I have had them occur just as frequently during the first injection as during subsequent ones. It is my belief that they are caused by injecting the solution too rapidly.

Before freshly distilled water was used severe constitutional symptoms beginning six to twelve hours after injection were frequent. They began with chills, followed by fever ranging from 101 to 105° F. in some cases, accompanied by nausea, vomiting, diarrhea, etc. With the present improved methods of administration these reactions are either mild or absent. They are rarely more severe than a slight nausea, occasional vomiting, and a rise of one to two degrees in temperature.

Intramuscular Injections of Salvarsan.—Intramuscular injections of salvarsan were formerly given in alkaline solution and in neutral suspension. These injections were very painful and caused large indurations which frequently broke down and formed abscess. The method of choice at the present time is a suspension of the powder in an oily vehicle.

EQUIPMENT

Small mortar, capacity 1 oz.

Glass stirring rod.

Record syringe, 10 c.c.

Needle, 1½ in. long, gauge 14.

PREPARATION OF OILY SUSPENSION.—Strict asepsis must be observed throughout. The instruments must be carefully boiled before using. The

ampule of salvarsan is placed in 95 per cent. alcohol and wiped dry with sterile gauze. Any bland sterile oil may be employed, such as ol. sesame, or ol. amygdal. dule. The writer prefers iodypin, 10 per cent. This is an iodine addition compound of sesame oil and makes an excellent vehicle. Five c.c. is used for 0.6 gram.

The salvarsan powder is rubbed up with the oil in the mortar until a smooth suspension is obtained. No alkali or water is added.

PREPARATION OF PATIENT.—The most favorable site of injection is in the upper and outer quadrant of the gluteal region. The region of the sciatic nerve must be carefully avoided. Some make the injection in the lumbar muscles, selecting a point about three inches above the iliac crests. The skin is sterilized by painting with iodine.

Having selected the site of injection, local anesthesia is obtained by injecting, intradermically, a few drops of either 4 per cent. novocain or 2 per cent. alypin until a small wheal is raised. The needle is then inserted deeply into the gluteal muscles and 1 c.c. of the anesthetic injected. Anesthesia is produced in 5 minutes.

TECHNIQUE OF INJECTION.—The needle used is 1½ inches long and 14 gauge.

The needle is quickly introduced through the skin deeply into the gluteal muscles. The surgeon should wait a few moments to determine if a blood vessel has been entered or punctured, in which case blood will escape from the needle. Should this occur, withdraw the needle, flush it out and insert in a different direction. The injection is then made very slowly to avoid trauma and hemorrhage in the muscles. During the injection the patient will sometimes complain of pain radiating down the thigh to the inner side of the knee.

After injection the part is gently massaged and the puncture wound painted with collodion. As the effect of the local anesthetic wears off, pain begins to be felt, increasing gradually until it may become intense. Some are relieved by heat in the form of hot water bags or hot compresses of lead and opium. Morphine is rarely necessary. The following will be found useful to relieve the pain:

R Codein Sulphategr. ¼
 Pyramidon
 Aspirināā grs. v
 M. Ft. Cap.
 Sig. One capsule every four hours.

AFTEREFFECTS.—Within a few hours swelling begins in the injected area, reaching its height in about 36 hours. It then gradually subsides so that in about two weeks the induration is reduced to a small nodule, which slowly disappears.

DOSAGE OF SALVARSAN.—The average doses for intravenous injection are as follows:

For women, 0.3 to 0.4 gram.

For men, 0.4 to 0.5 gram.

Formerly the maximum dose, 0.6 gram, was frequently given. Many observers now believe that equally good if not better results are obtained with does not exceeding 0.4 gram. This is also my belief. I find that with this dosage the drug is better borne and can be much more frequently administered.

For intramuscular injection the dose is somewhat larger, ranging from 0.3 to 0.6 gram.

NEOSALVARSAN

Neosalvarsan is a true derivative of salvarsan. It is a condensation product of formaldehyd sulphonylate of sodium and salvarsan. It contains less arsenic than salvarsan, 1.5 grams corresponding to 1 gram of salvarsan.

It is administered intravenously and intramuscularly.

Intravenous Administration of Neosalvarsan.—**PREPARATION OF THE SOLUTION.**—The preparation of the neosalvarsan solution is much more simple than that of salvarsan. All that it requires is the addition of water, whereupon it immediately dissolves, giving a transparent yellow solution of neutral reaction. Vigorous shaking is to be avoided, to prevent the formation of poisonous oxidation products. Freshly distilled water or saline 0.4 per cent. at room temperature is used. The writer employs only distilled water. The temperature of the water must never be above 20 to 22° C. (68 to 71° F.).

Formerly, 25 c.c. of water were used for each decigram of the drug. This amount has gradually been reduced so that at present it is administered in concentrated solution.

Ravaut, Emery and Duhot were among the first to employ concentrated solutions. Great care must be exercised in making the puncture, to insure against injecting the solution into the subcutaneous tissues. The writer employs 2 c.c. of water for each decigram of neosalvarsan.

The required amount of freshly distilled water is placed in a small beaker and the neosalvarsan added. Shake a few times gently until the powder is completely dissolved. The solution is ready for use and is injected with either a 20 c.c. Luer or Record syringe.

The preparation of the patient, technique of injection and aftertreatment are the same as for salvarsan.

The reaction after injection is either very mild or absent. The temperature may rise to 100° F. Nausea, occasional vomiting and slight diarrhea may occur. Rarely, a rash appears about the fifth day, gradually disappearing in a few days.

DOSAGE OF NEOSALVARSAN.—

For men, 0.3 to 0.9 gram.

For women, 0.45 to 0.6 gram.

For children, 0.15 to 0.3 gram.

Intramuscular Injection of Neosalvarsan.—At first, neosalvarsan was injected in watery solution. These injections were so painful that they are rarely given at present. The writer has found the glycerin suspension the most satisfactory.

PREPARATION OF GLYCERIN EMULSION.—In a small mortar place 3 c.c. of chemically pure glycerin. Add the neosalvarsan powder and gently stir until a smooth suspension is obtained. Add 15 drops of a 1 per cent. alypin solution. The addition of the anesthetizing solution causes some of the powder to dissolve, rendering it more suitable for injection.

The preparation of the patient is the same as described under salvarsan. The technique of injection and aftertreatment are also similar.

Intraspinal Injections of Salvarsan and Neosalvarsan.—The treatment of cutaneous, visceral and bone syphilis with salvarsan in combination with mercury and iodin has proven very satisfactory. Syphilis of the nervous system has responded much less favorably. With a view to a more radical attack upon the disease, the introduction of salvarsan directly into the cerebrospinal fluid suggested itself. For the detailed description of the various methods employed, the reader is referred elsewhere in this work.

Provocative Injections of Salvarsan.—Gennerich and Milan, working independently, observed that the Wassermann frequently became more positive after an injection of salvarsan. Also that in some cases a Wassermann previously negative became positive after salvarsan. Both observers found that when half doses were injected six months or a year after an apparent cure, a positive reaction was obtained if any infection remained. If the cure was absolute, the serum reaction remained negative.

The practical application of this test is one of the greatest advances in the management of syphilis, in that it makes the Wassermann reaction much more delicate, thereby revealing obscure and latent syphilis.

The test is performed as follows:—0.3 gram of salvarsan or 0.45 gram neosalvarsan are injected intravenously. Five days later a Wassermann is performed. If positive, treatment is resumed and kept up as long as a positive reaction is obtained after a provocative injection.

In my own cases, provocative injections gave positive reactions in about 20 per cent. As these patients were all Wassermann negative for six to twelve months after treatment was stopped, the value of the test becomes evident.

COMPARATIVE VALUE OF SALVARSAN AND NEOSALVARSAN

Experience has shown that, dose for dose, neosalvarsan is less effective than salvarsan. Castelli has proven in experimental syphilis that one unit of arsenic in the form of salvarsan did the work of two units of arsenic in the form of neosalvarsan. Clinically, the symptoms disappear equally well with both drugs, but the Wassermann reaction persists longer in patients treated with neosalvarsan. On account of its simplicity of preparation and the comparative freedom from disagreeable aftereffects, the latter is preferred by many, who though admitting the greater effectiveness of the older preparation, believe that the same results can be obtained with neosalvarsan by increasing the number of injections. In my own work, as nearly as I could determine clinically and serologically in parallel cases, five doses of neosalvarsan were equivalent to three of salvarsan given at the same intervals. In nervous hysterical women and in debilitated subjects, neosalvarsan is the preparation of choice.

Regarding the relative value of the intramuscular and intravenous methods, serological tests and clinical observation show that although the immediate effect of the intravenous injection is more prompt, it is less enduring, owing perhaps to its more rapid elimination. According to Craig of the United States Army, who has had an unusual opportunity to study the results obtained by both methods, one intramuscular injection seems to have more curative value than two intravenous given at short intervals. The pain and discomfort attending the intramuscular method have caused it to be practically abandoned at the present time.

USE OF SALVARSAN IN PREGNANT SYPHILITIC WOMEN

C. Sauvage sums up the effect of salvarsan as follows:

Intravenous injections of salvarsan have a remarkably favorable effect upon the accidents of syphilis operative during pregnancy.

It assures a healthy issue in most cases.

Latent syphilis, or cases which had been irregularly or insufficiently treated, when complicating pregnancy, should be treated with salvarsan.

Cases that have been rigorously treated before conception takes place and in which no active manifestations are present during pregnancy should be treated with mercury. Salvarsan, while possibly more efficacious, is more dangerous. Diseases of the liver and kidneys when complicating pregnancy are contraindications to the use of salvarsan.

TREATMENT OF HEREDITARY SYPHILIS

Immediate and striking results follow the injection of salvarsan in infants in whom mercury had been used with little or no apparent benefit.

Dosage.—The dose for infants up to 8 months varies from 0.01 gram to 0.05 gram salvarsan (0.01 gram-0.075 gram neosalvarsan). Above 8 months, from 0.075 to 0.2 gram is given according to age and tolerance.

The initial dose should always be small and if well borne gradually increased in succeeding injections. In case of extreme wasting, pemphigus, etc., the initial dose should not exceed 0.01 gram.

Holt injects the drug properly diluted into the external jugular vein, using a 22 gauge needle, 1.5 cm. long, attached to a 5 c.c. Luer syringe.

CONTRAINDICATIONS TO THE USE OF SALVARSAN AND NEOSALVARSAN

Speaking generally, any marked organic disease of the heart, arteries, liver and kidneys is a contraindication, if the lesions are nonsyphilitic in origin. If they are syphilitic, it will depend upon the stage of the disease. Thus, the nephritis of early syphilis can be safely treated with salvarsan because it is not a true nephritis and does not prevent the excretion of arsenic. In true nephritis and in late syphilitic nephritis, the drug should not be administered.

Advanced hepatic cirrhosis is a contraindication in that, owing to excessive destruction of the parenchyma, rapid excretion of arsenic is prevented. In gummatous disease of the liver, it is best to start the treatment with mercury and iodine, after which neosalvarsan may be administered, beginning with small doses.

In cardiac and arterial syphilis, experience has taught us the following:—early cases of aneurism are improved by neosalvarsan, relief being also obtained in later cases by the cautious use of the drug; early myocarditis is not a contraindication. In all late cardiac syphilis, especially syphilitic aortic disease, salvarsan should not be administered on account of the frequent accompanying coronary involvement. The slight reactionary inflammation following injection may produce obliteration of the arteries and cause sudden death.

All nonsyphilitic inflammatory ophthalmic disorders are contraindications.

Special caution must be taken with patients presenting evidence of early specific meningitis or any nervous condition due to recent syphilitic invasion. The early and too frequent administration of salvarsan in these cases has caused death due to hemorrhagic encephalitis. It is best to begin with mercury and, after the nervous symptoms have subsided, start with small doses of neosalvarsan, gradually increasing the dose at five-day intervals.

For the management of late syphilis of the nervous system the reader is referred elsewhere in this work.

Nonsyphilitic lesions of the eighth nerve and those due to late syphilis are made worse by salvarsan. Cases have been reported in which old

syphilitics with nerve deafness became stone deaf after salvarsan, while on the other hand patients in whom the deafness was nonsyphilitic had the deafness increased by salvarsan.

NEURORECURRENCES

The frequency of lesions of the cranial nerves, especially the second and eighth, after the use of salvarsan, led to the belief that they were due to an arsenical neuritis. Their apparent frequency of recurrence after salvarsan led syphilologists to examine their cases more thoroughly before treatment, with the surprising result that the frequency of such lesions was nearly as great as those reported due to salvarsan. They noticed also that these nerve affections were most common in the first year of the infection and that they occurred just as frequently in patients who had not had any mercury as in those who had. This tends to prove that these neurorecurrences are not due to salvarsan, but are true syphilitic meningeal lesions. As a result of syphilitic inflammation, the meninges increase in size and produce pressure upon the nerves as they pass through the bony canals. This pressure at first causes neuritis and, if continued, atrophy.

The fact that they are improved or entirely relieved when intensive treatment with salvarsan and mercury is promptly resumed is a further proof that they are a syphilitic recurrence, due to inadequate treatment.

Mercurials Employed.—For the detailed consideration of the various salts of mercury and the methods of administration, the reader is referred to the preceding article.

SUMMARY ON TREATMENT OF SYPHILIS

No hard and fast general rules can be given as to the amount and duration of treatment required to cure syphilis, because of the protean nature of the disease, appearing as it does in so many different forms and varying degrees of severity. Other important factors likewise influence the management of this disease. Briefly stated they are:—the age, sex, general condition, habits, previous treatment, and finally, the response to and tolerance for treatment.

It is evident from the foregoing that the treatment will depend entirely upon the type of case. Although no one can say in a given case how long or how much treatment will be necessary, it is advisable to have some general plan of procedure when beginning the treatment. The writer employs the following régime, subject to change as special indications arise.

1. **PRIMARY STAGE;** characterized by the initial chancre and a negative Wassermann reaction.

First week,	0.3	gram	salvarsan	intravenously
Second "	0.4	gram	"	"
Third "	0.4	gram	"	"
Fourth "	0.4	gram	"	"

Follow with an intensive course of mercury by injections for five months. If no clinical symptoms are present, stop treatment for six weeks and perform a Wassermann test. If negative, do a provocative test, two weeks later. If positive proceed as outlined under (3).

2. STAGE OF PRIMARY CHANCRE with evidence of general invasion as shown by a positive Wassermann, but with no other clinical symptoms of the secondary stage.

Begin treatment with four intravenous injections of salvarsan as outlined in (1) and follow with mercury intensively for five months. At the end of six months perform a Wassermann. If positive give four more injections of salvarsan and five more months of mercury. If negative, continue the mercury for six months. At the end of the first year, tests to determine a cure are carried out as described under (3).

3. STAGE OF GENERALIZATION as shown by a positive Wassermann and the usual secondary clinical symptoms.

First week,	0.2	gram	salvarsan	intravenously
Second "	0.3	gram	"	"
Third "	0.4	gram	"	"
Fourth "	0.4	gram	"	"
Fifth "	0.4	gram	"	"
Sixth "	0.4	gram	"	"

Continue with mercury up to the seventh month. Perform a Wassermann without stopping treatment. If positive, give four more intravenous injections and five months of mercury. If negative, continue with mercury alone up to end of first year. Stop treatment for six weeks and perform a Wassermann. If negative, do a provocative test, two weeks later. If the provocative test is positive give another series of four injections of salvarsan supplemented with five months of mercury, after which tests are again made. Treatment must be kept up until the provocative tests become negative, after which an ordinary Wassermann is made every three months during the year following. If they remain negative a final provocative test is made. If that is also negative, the case is discharged as cured.

At the end of the first year the cerebrospinal fluid should be examined. If it shows pathological changes the question of intraspinal treatment comes up. The indications and technique of administration are considered elsewhere in this work.

4. RECURRENT CASES. The treatment of these cases is carried out along the same lines as indicated under (3).

CHAPTER XXV

TUBERCULOSIS

HERBERT MAXON KING

500. Line 22 *read*:

citing gastric disturbance. **Intravenous injection of 5 to 10 c.c. of a hypertonic salt solution (10 per cent.) in some cases is effective, apparently increasing the coagulability of the blood.** Ergot and adrenalin, from the fact that they

Line 27 *read*:

is to take place. **In cases of continued slow oozing of small amounts of blood they do at times appear to be of value.** [They also cause contraction of the muscularis of the

501. Line 3 *add* after "purpose.":

Horse serum, subcutaneously in doses of from 20 to 40 c.c., is sometimes used with the same object in view. It may give rise, however, to disagreeable skin eruptions or other anaphylactic phenomena, especially if the doses are repeated.

Line 28 *add* after "ineffectual.":

[Emetin hydrochlorid, gr. $\frac{1}{2}$ to 1, given hypodermatically, has been found to stop hemoptysis. It may be repeated in four hours. The *modus operandi* is not known, but the result is very satisfactory.—EDITOR B.]

504. Line 31 *read*:

ment the appetite usually improves greatly. A **bitter** tonic, such as

505. Line 24 *read*:

he desires. **Ichthoform, best given in capsules in doses of from 5 to 10 grains three or four times a day, sometimes affords relief for a time.** Bismuth often relieves the symptoms somewhat, but for the

535. Line 34 *add* after "-cess.":

The closed method is the one that is being used almost exclusively, at least in the United States, at present. It is simpler, much less trouble-

some to the patient, and, if carefully used, probably fully as safe as the open method.

536. Line 10 *add* after "side.":

In determining this point both physical and X-ray examinations should be used. Many cases, however, which show considerable mottling of the good side on X-ray plates, do well under the treatment, provided the physical signs do not denote any activity on that side.

Lines 17-18 *read*:

conforming to the above requirements, offer an indication for the trial of the method. **Febrile cases, if still progressing unfavorably after a trial of hygienic treatment, should if unilateral be given the benefit of this treatment.** Some truly marvelous results in the clearing up of

Line 21 *add* after "pneumothorax.":

It should be used in hemorrhage cases only when it can be determined with reasonable certainty which side the bleeding is on. This can often be determined by the stethoscope, bubbling râles appearing in one side during or after the bleeding. Many patients also have a definite sensation that the blood is coming from one side. If the patient is intelligent and not too hysterical, considerable reliance may be placed on this sign. If previous physical or X-ray examinations have shown that one side is extensively involved or with cavity, and the other side clear or only slightly involved, it is safe to assume that a large hemorrhage is coming from the bad side.

537. Line 5 *read*:

Dr. Samuel Robinson of **Rochester, Minn.**, and is the one used at the Loomis

Lines 16-18 *read*:

Nitrogen gas **has usually been used on account of the supposed slowness of its absorption. Experiments by Webb of Colorado Springs, however, would indicate that such a diffusion of gases soon takes place through the pleura that the ultimate composition of the gas within the pleural cavity becomes the same, whether nitrogen or air be used. Atmospheric air may therefore be used and will probably give the same results as nitrogen.**

Lines 40-44 *read*:

On reinjection greater and greater amounts may be used until **as complete collapse of the lung as possible** is obtained.

Reinjections should be made at frequent enough intervals to offset absorption of the gas and expansion of the lung. This can be best determined by **frequent careful physical or fluoroscopic examinations.** Ordinarily the injections

538. Line 2 *read*:

longer intervals will be sufficient. **As a rule it is not advisable to wait**

longer than one month between injections, for fear that expansion will occur and pleural adhesions take place, preventing subsequent collapse. The length of time during which the

Lines 8-10 (B. F.) 8-9 (F.) *substitute*:

As long as the patient is improving under the treatment, it should be maintained, and most observers deem it wise to continue the collapse for a long time even after the disease is apparently arrested.

Not infrequently the appearance of a pleural effusion will put a stop to further injections. In these cases some physicians withdraw the fluid and substitute gas. This does not seem advisable, however, as the fluid serves the same purpose as the gas in compressing the lung and there is much more danger of producing an infection than there is in a dry pleura.

If artificial pneumothorax treatment is employed judiciously, especially in the selection of cases, striking results can be obtained by means of it. Seemingly hopeless cases have sometimes been arrested. In cases which are favorably influenced by it, the most striking results are the quick loss of fever, the decrease of expectoration, and often ultimately the clearing up of tubercle bacilli from the sputum.

561. *Add* under "References.":

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CHAPTER XXVI

ROCKY MOUNTAIN SPOTTED FEVER

REVISED AND REWRITTEN BY

JOHN F. ANDERSON

Rocky Mountain spotted fever is an acute infectious disease characterized clinically by headache, pains in the back, joints and extremities; fever of a remittent type; an eruption, at first macular, later becoming petechial, and with a tendency to gangrene of certain parts of the skin. The disease is transmitted by the bite of an infected tick.

The disease occurs in the Rocky Mountain and Pacific states, east of the Coast Range Mountains. The great majority of cases occur during the tick season, from early spring to midsummer. The first cases are usually noted after the snow melts, and increase in number as spring advances. The virulence of the disease shows marked variations for different sections, as is shown by the high case mortality in the Bitter Root Valley of Montana, and the comparatively low mortality in the region of the Snake River in Idaho.

The researches of Ricketts, King, McClintic and of Fricks have conclusively demonstrated that Rocky Mountain spotted fever is transmitted by the bite of the wood-tick, *Dermacentor Andersoni*. The work of these investigators has shown the presence of infected ticks caught at large and that the reservoir of infection is probably in the small wild animals of the infected regions.

While we know that the tick transmits the disease we, as yet, do not know the specific etiological agent, so that the statement of Ricketts still holds that the disease is "a generalized invasion of the body by a micro-organism which, as yet, is unrecognized and uncultivated."

The disease bears a close clinical resemblance to typhus fever, and cases of the two diseases occurring in the same locality would be, at the bedside, difficult to differentiate. Fortunately the inoculation of the guinea pig with blood from a spotted fever case induces in that animal,

with great regularity, a characteristic reaction so that the diagnosis can be satisfactorily determined.

While Rocky Mountain spotted fever has been observed for a great many years and a great many suggestions have been offered for the treatment of the disease, we are, as yet, without knowledge of any specific treatment. But the fact that the researches of the last ten years have shown the manner in which the disease is conveyed has enabled us to formulate measures which offer distinct promise of the eventual control and perhaps eradication of the disease.

The treatment of the disease is best discussed by first taking up the measures for the prevention of the disease, and then those for the treatment of the individual after the onset of illness.

PROPHYLAXIS

By reason of the fact that the disease is conveyed by the bite of an infected tick, all our measures for the prevention of the disease are focused upon ways to prevent persons being bitten by those insects and upon the eradication of ticks in endemic foci of the disease.

Before we take up the general or community measures which have for their object the eradication of the ticks, we shall consider those prophylactic measures which apply to the individual. The first of these is avoidance of localities, so far as possible, within the endemic foci of the disease during the tick season.

For those who must enter the infected region certain precautions are suggested. They should avoid as much as possible personal contact with brush, weeds, grass and animals which now harbor ticks. Tickproof clothing should be worn and the clothing and body should be examined as often as possible to see that no ticks are thereon. If a tick is found attached to the body it should be at once removed and the site should be cauterized immediately with 95 per cent. carbolic acid. Care should be taken in removing the tick not to leave the head embedded in the skin. The tick may usually be readily removed by applying ammonia water, turpentine, liquid petrolatum, or kerosene, and it should be at once destroyed as it has been demonstrated that the bite of a single tick may transmit the disease.

The really brilliant work of the Bureau of Animal Industry in limiting and decreasing the spread of Texas fever of cattle, which disease is also conveyed by ticks, has shown what may be hoped for in our efforts to control Rocky Mountain spotted fever. These efforts all have for their object the decrease in the tick population. As the stock furnish a food supply for the tick during the various phases of its life history, and as the female tick is fertilized during feeding, the killing of ticks on cattle,

horses, and other stock, by "dipping" in some approved "dip," is of great importance. The dipping of all stock in the region of the disease should be required by law from early spring to midsummer. The clearing of the land of brush and then burning will destroy large numbers of ticks and their eggs.

Fricks in 1913 showed that even when ticks are placed in the wool of sheep they soon die, and in later papers he has brought out convincing data as to the importance of sheep grazing over infected land for the destruction of ticks. He considers that the grazing of sheep results in the removal of undergrowth and the destruction of "good tick country" by close grazing, in the removal or disappearance of other large mammals, both domestic and wild, from the sheep range; and in the destruction of ticks by the grazing sheep; and finally, it places the problem of tick eradication on an economic basis.

As investigations have shown that the small animals of the infected region may harbor large numbers of ticks, and may also be susceptible to the disease and thus maintain a reservoir of infection for ticks, it becomes of great importance that the number of small animals be reduced as much as possible. For this reason bounties should be offered for the killing of the small animals, particularly the ground squirrel, chipmunk, and others.

TREATMENT

There are few diseases for which more drugs have been recommended than for spotted fever and as yet we are without a satisfactory specific treatment, although attempts have been made to produce a serum for this purpose. Ricketts used a serum prepared from the horse by immunizing with blood from infected guinea pigs; the serum was found to have some protective properties and also apparently exerted some influence on the developed disease in guinea pigs, when given early and in large doses. Results of its use in human cases did not offer much promise of its value.

From the time of the bite by an infected tick to the development of definite symptoms, there is an incubation period of from three to nine days, during which time, or most of the time, the patient may feel entirely well, or he may experience obscure and indefinite sensations, especially constipation and more or less headache and general malaise. At this time the patient may not know that he has been bitten by a tick, the tick or tick-bite (if the tick has fed and dropped off) often not being discovered until the characteristic symptoms develop. Usually, when the physician first sees these cases, the patient is complaining of considerable headache and pains in the legs, back, etc., and has from one to three degrees of fever. In the Montana cases, however, the pains are not a very prominent early symptom (Dodds).

When first seen the patient should be given a hot bath and ordered to bed. A generous dose of *calomel* and *soda*, to be followed by an efficient *saline*, should be given at once, and the patient instructed to *drink freely of water*.

A great number and variety of drugs have been suggested for the relief of the *pains* which are a more or less constant accompaniment of this disease, especially during the first ten days. Probably the best remedy for the relief of the pains is *aspirin* (McCalla, Mills, Numbers, Smith, Springer, Stewart), in doses of 0.32 to 0.65 gm. (5 to 10 grs.), repeated every two to four hours. The size and frequency of dose should depend entirely on the effect it has on the pains, care being exercised to avoid overdosage and to follow each dose with a copious draft of water. Phenacetin (Bowers, Dodds, McCalla, Numbers, Shirley, Smith, Taylor), salol (Shirley), and the salicylates (Bowers, Mather, Mills, Numbers) may also be used, while some physicians resort to the use of acetanilid (Taylor), the bromids (Numbers, Springer), quinin (McCalla, Mooser, Taylor), and antipyrin (Springer), in varying dosage and combinations. In the more malignant type of the disease some use dry heat, or sponge the patient with a hot 2-5 per cent. solution of phenol (McCullough), and more frequently resort is made to the use of morphin (Dodds, Kellogg).

In the writer's opinion, however, it is rarely necessary or advisable to prescribe morphin or other form of opiate in these cases. If the bowels have been properly cleansed, there are few cases that will not be made comfortable by the intelligent use of aspirin and hot baths (Bowers, Mills), or dry heat.

If the remedies given to relieve the pains are not also sufficient to keep the *fever* within reasonable bounds, *hydrotherapy* (Bowers, Dodds, McCalla, Mills, Numbers, Pease, Smith, Springer, Stewart) may be resorted to with confidence. Cold sponge baths and cold packs are sufficient in most cases of hyperpyrexia; tubbing can be used where these fail to reduce the temperature. Mills recommends bathing the patient in hot water, gradually bringing the temperature of the water up to 120° F.

In severe cases the eruption is often marked in the throat and on the palate, and the mouth, tongue, and throat are dry, foul, and distressingly uncomfortable. In such cases a mild antiseptic mouth-wash, containing also glycerin and perhaps lemon juice, if used frequently as a gargle or swabbed over the parts, will contribute materially to the patient's comfort.

As *constipation* is practically always present during the entire course of the disease, a gentle laxative should be exhibited daily. Nothing serves better for this purpose than the *sulphate of magnesia* (Smith, Springer, Stewart), in sufficient doses to produce one or two daily stools.

Regardless of the fever, the nurse should be instructed to give the patient frequent sponge baths, followed by alcohol rubs, to maintain an

active and comfortable condition of the skin, and the position of the patient should be changed frequently to prevent hypostatic congestion and slough formation. If the skin itches or burns, sponging with a strong soda solution, or applying an ointment of oil of eucalyptus, one part in eight parts of vaselin (Springer), will be cooling to the skin and relieve the itching.

The *heart* often shows signs of weakness and dilatation, particularly in the older patients, and this condition calls for the exhibition of *digitalis* and *strychnin*, preferably given hypodermically. Taylor advises the routine use of strychnin as soon as the pulse rate begins to rise, to be continued through convalescence to support the weakened heart muscle.

Bronchitis complicates many of the cases, and in alcoholics pneumonia is liable to occur (21). Edema of the lungs is also reported as a fatal complication (8; 22). Cases having lung complications require special care in nursing, frequent change of position in bed, and otherwise attending to the comfort of the patient and to the hygiene of his environment. The heart usually goes bad in these cases and needs constant watching. Whiskey, egg-nog, etc., may have to be given in addition to digitalis and strychnin to stimulate and support the heart, and oxygen may be of benefit in combating the carbonic acid poisoning.

Nephritis is not a common complication, but nearly all of the severe or fatal cases develop uremia, or at least a profound toxemia. Hence the advisability of encouraging all patients to drink freely of water, and also the daily exhibition of moderate doses of magnesium sulphate or other laxative. In the severe cases, if the patient's condition will permit of it, the hot bath or hot pack will be of benefit by promoting activity of the skin and relieving the overtaxed kidneys. The slow saline enemata, drop-method (Pease), or normal salt solution given subcutaneously, may be of special service.

In the Montana cases cerebrospinal symptoms are frequently encountered (Kellogg), and delirium is practically always present in the severe cases. One case is reported (21) where the patient developed an acute mania which lasted about two months after convalescence. Hydrotherapy, sedatives, and restraining measures limit the physician's usefulness in these cases.

When the eruption involves the palate and pharyngeal walls, as it sometimes does in the Idaho cases, gangrene is apt to develop and prove a serious complication, practically always fatal. In addition to the cleansing and antiseptic mouth wash suggested above, removal of the necrotic tissue may make the mouth less foul, and thus add to the patient's comfort. Gangrene of the scrotum and lobule of the ear may develop in the very severe cases, the treatment being surgical.

The early and continuous use of quinin in large doses is recommended by Anderson, Mooser, and Taylor, with the claim that it has a favorable

influence on the course and severity of the disease, but this claim is not sustained by the experience of many other physicians.

In using the quinin treatment it is recommended that the sulphate be given in 1.0 to 1.32-gm. (15 to 20-gr.) doses, repeated every four to six hours. If the sulphate disturbs the stomach, the bimuriate may be given hypodermically, 1.0 gm. (15 grs.) every six hours (Anderson), or the quinin may be combined with sodium benzoate, 1.0 to 1.32 gms. (15 to 20 grs.) of the former to 2.0 to 2.65 gms. (30 to 40 grs.) of the latter per day (Taylor). Mooser gives 2.0 gms. (30 grs.) twice daily for about one week, then gradually reduces the dose until temperature remains normal. Kellogg and Reed have each used sodium cacodylate with apparent success in a single case.

The *diet* requires careful supervision from the beginning of the disease to prevent intestinal fermentation, and later to properly sustain and nourish the patient. If the bowels are kept open a fairly generous *soft diet* may be allowed most patients throughout the entire course of the disease. Milk, buttermilk, sauer milch, or Bulgarian buttermilk, kumyss, broths, soft eggs, soft toast, etc., are usually well borne and relished by the patient, and can be repeated every two to four or six hours.

SUMMARY

To summarize, the chief features in the treatment of spotted fever are as follows:

1. Preventive measures, by avoiding exposure to infection, and the various methods for destroying ticks.
2. Initial dose of calomel and soda, followed by a saline.
3. Aspirin for pains.
4. Hydrotherapy for fever.
5. Sulphate of magnesia daily, and drink freely of water.
6. Strychnin, digitalis, and whiskey for weak heart.
7. Soft diet.
8. Bitter tonics, hydrochloric acid, and iron in convalescence.

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CHAPTER XXVII

WEIL'S DISEASE

ALLAN RAMSEY

570. Line 15 *add* after "naturally.":

[Japanese investigators have recently (1916) described a spirochete (*Spirochaeta icterohemorrhagial*) obtained from patients suffering from a disease corresponding, clinically, to Weil's disease. On the basis of this discovery, they discuss the etiology, prophylaxis and therapy of the disease.—EDITOR B.]

573. *Add* under "References.":

Inada, Ido, Hoki, Kaneko, and Ito. Jour. Exper. Med., 1916, XXII, 377; 1916, XXIV, 471, 485.

Moritz. Brit. Med. Jour., London, 1915, II, 602.

Osler. Lancet, London, 1915, II, 605.

CHAPTER XXX

FOOT AND MOUTH DISEASE

ALLAN RAMSEY

This is an acute infectious disease of animals which is occasionally transmitted to man. Its cause has not as yet been discovered, but it is both directly and indirectly contagious for human beings. Among the lower animals the disease prevails in epidemic form, the extent and ravages of some of the epidemics being tremendous. It occurs frequently and extensively in the European countries, but in this country it is rare. In Germany, in 1892, there were 4,153,539 domestic animals affected; the following year there were 500,342.

In man foot and mouth disease usually occurs sporadically, but occasionally it appears as an epidemic. Considering that the disease is communicable to man, and that the epidemics among animals are so extensive, it is astonishing that the disease is so rare with human beings.

While the specific cause of the disease has not as yet been found, the infectious material exists in the liquid contents of the vesicles, in the secretions from the ulcers, in the milk tainted by the vesicles and ulcers, and possibly in the urine and feces.

The lymph from the vesicles, when inoculated into calves, promptly produces the disease. Nevertheless, no bacteria can be found in this lymph either by the microscope or by cultural methods. The lymph can be filtered through the finest porcelain filter, and it still retains its virulence. The virus must, therefore, belong to the ultramicroscopic, and in this respect is similar to that of such diseases as smallpox, scarlet fever, and measles. It is the most infectious and virulent toxin or virus known among animals.

Prophylaxis.—Prevention of this disease is of the first importance and the prophylaxis of the disease in man is naturally closely connected with that of the disease in animals. At the present time prophylaxis among the domestic animals means chiefly the limiting and stamping out of the disease after it has made its appearance. There is no successful

method of direct treatment of the disease itself. Vaccination has been tried, but up to the present time no satisfactory vaccine has been devised.

The following illustrates much that is of interest in both the subjects of prevention and transmission. In November, 1908, an outbreak of foot and mouth disease was discovered among some Pennsylvania cattle. A prompt investigation of the epidemic by the Federal Government disclosed the fact that some of the smallpox vaccine virus, imported from a foreign country, was contaminated with the disease. When this vaccine was employed for the production of vaccine in calves, the calves became infected with the foot and mouth disease. This occurred with only one concern manufacturing biologic products; from this concern another purchased the contaminated vaccine and infected its own calves. The calves of the second firm, which were now infected with the foot and mouth disease, were finally sold in the open market and they started the epidemic. The calves of the first firm, after they had served their purpose for the production of smallpox vaccine, were killed by the firm in accordance with its usual custom of dealing with its own animals.

The Government immediately withdrew the license of both these firms, all their smallpox vaccine was at once recalled from the open market, and by other vigorous measures also the epidemic was promptly checked and eradicated. This one episode cost the Federal Government \$300,000.

No instance of foot and mouth disease communicated to man through smallpox vaccine has been recorded.

The disease in cattle is to be dealt with by means of slaughter of infected and exposed animals, by quarantine and by disinfection of stables and premises involved. Slaughter, combined with quarantine and disinfection, is the method in the United States; in Germany, where the disease is endemic, this method is too costly and would destroy too large a part of all her animals. In our country the Federal Government pays one-half and the State Government the other half of the value of the animals destroyed. In this country in 1914 we had our most severe and most extensive epidemic, which was handled by these methods.

Prophylaxis in man involves the following measures: First, the patient should be isolated. Among a dairy or peasant population this is not easy. Persons with cuts or erosions upon their hands should abstain from milking diseased cows. Secondly, the milk from infected cows should be boiled as such milk is capable of producing the disease. During epidemics it would probably be best to boil all milk and thus reduce the danger to the minimum. Meat from infected animals should be boiled; butter, cream and cheese from such sources should not be used at all.

Treatment.—The general treatment is dietetic and symptomatic, and requires no description. Attempts at a prophylactic serum are not yet

successful, although Loeffler and Frosch have done much valuable work in this direction.

The chief treatment is directed to the care of the inflammatory condition about the lips and mouth; efforts should be made to give relief from the pain and to prevent secondary infection of the ulcers. This is accomplished by touching each ulcer with nitrate of silver. Baginsky advises the use of a one-third per cent. solution of permanganate of potash. A two per cent. solution of chlorate of potash may be employed as a gargle.

Fatalities are rare, and when they do occur they are found most frequently among children.

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Frothingham. Boston Med. and Surg. Jour., 1903.
Leffler. Münch. med. Wochens., 1897.
—— and Frosch. Deutsch. med. Wochens., 1905.
Ohler. Münch. tierärztl. Wochens., 1915, LXVI, 649.
Public Health Reports. Wash., XXX, Mar. 26, 1915.
Résumé U. S. Government Report. Jour. Am. Med. Ass., 1909.
Siegel and Bussenius. Deutsch. med. Wochens., 1897.
Stierlin. Münch. med. Wochens., 1897.
U. S. Dept. Agriculture. Farmer's Bull., Apr. 22, 1915.

II. THE INTOXICATIONS

CHAPTER I

ALCOHOLISM

A. D. BLACKADER

589. Lines 41-44 *read*:

a mixture containing **bismuth carbonate** and sodium bicarbonate with **nux vomica** forms our best corrective. Should the condition be one of atony, strychnin, with or without a mineral acid, and combined with capsicum, will give good results. **The following combination has given excellent results in some cases:**

Add after line 44:

R	Sodii bicarbonatis	℥ii	8.00
	Sp. ammoniæ aromatici	℥vi	24.00
	Tincturæ nucis vomicæ.....	℥iv	16.00
	Tincturæ capsici	℥iv	16.00
	Elixir aromat	℥i	30.00
	Agriæ ad	℥vi	180.00
	Misce et signa		

One dessertspoonful in half a wine glassful of water every three or four hours.

590. Lines 25-26 *read*:

narcotic rapidly develops. **In many minor ailments temporary benefit may frequently be obtained from the use of alcohol.** In many gas-

591. Line 25 *add* after "lost":

Still later more severe mental disturbances may set in, characterized by hallucinations and delusions and even profound dementia.

594. Lines 27-28 *read*:

More successful results may be obtained in a properly **managed** sanatorium into which the patient enters **of** his free will and with a deter-

Line 33 *read*:

The patient is treated as one suffering from a **toxic** neurosis. The

Lines 37-38 *read*:

first few days complete rest in bed **is ordered** in a quiet, well-ventilated, and more or less darkened room; **an efficient cholagogue cathartic is administered, and repeated at such intervals as may be deemed desirable**; and a simple nutritious dietary, suitable

595. Lines 22-23 *read*:

in one or two hours, or a full dose of one of the hypnotics **may be administered** with the exception of chloral, whose toxic action on the heart muscle is to be feared.

599. Lines 11-13 *read*:

capable attendant, and where he unconsciously will exert more self-control than in his own home. The essentials of treatment which cannot be altered are the persistent administration of the belladonna mixtures in small doses, and thorough elimination, for which mercury, either as calomel or blue pill, appears to give the best results. A cholagogue action is essential and if the stools become clay-colored, ox gall, in some form, is recommended by Lambert. The treatment appears to be a very drastic one, but in actual practice it is surprising to see how even the most weakly and poorly nourished are able to stand it and go through with it, and when it is completed at once begin to gain weight, sleep well, and return to normal conditions. Regarding the method, Lambert writes as follows: "This treatment is not an infallible cure

Line 19 *add* after "relapse."

The use of cigarette smoking should also be interdicted as having a very definite influence in producing a craving for alcoholic stimulation.

601. Line 1 *read*:

In the treatment of **periodic alcoholism** very little can be done during

Lines 9-10 *read*:

for alcohol for some hours. The dose produces a slight pallor with an evanescent sense of

Line 12 *add* after "necessary.":

More efficient as a rule is a combination of small doses of apomorphin with strychnin and hyoscin given hypodermically.

	gm. or c.c.	
Apomorphinae hydrochloridi	.002	gr. 1/30
Hyoscinae hydrobromidi	.0006	gr. 1/100

	gm. or c.c.	
Strychninæ sulphatis	.002	gr. 1/30
Aquæ distillatæ	1.00	m. 15 Solve
Signa. To be given as a hypodermic injection.		

The general measures recommended on page 594 should always be enforced.

In many of these cases cigarette smoking is carried to excess and this fact is regarded by some physicians as an important exciting cause of these recurring attacks. Undoubtedly excessive cigarette smoking induces a nervous instability which in a peculiar way appears to crave alcoholic stimulation. Such patients, however, are exceedingly intolerant of alcohol and after one or two drinks they lose control of themselves and go on the full spree. To break this vicious circle the excessive use of tobacco, and especially of cigarette smoking, must be interdicted.

Spitzig regards this recurrent craving for alcohol as in some instances due to a defective intake of carbohydrates owing to the fact that the alcoholic uses little or no sugar and a lessened amount of starchy food. To destroy the craving he insists upon a maximum amount of cereals and sugar in the dietary. In those cases where there is a distaste for sugar, he orders a drachm of lactose every three hours in the form of a medicinal powder.

602. Lines 13-14 *read*:

that it can be used in distinctly larger amounts, and in such **cases** it is a food readily appropriated by the heart muscle

Lines 29-31 *read*:

bicarbonate, and should be followed in a few hours by an efficient saline. **Catharsis, however, must not be too violent.** Hot water should be given freely to drink, **to which may be added a little solution of ammonium citrate; about two drachms to the small tumblerful of water.** In other cases, **a weak cream of tartar lemonade may be preferred.** Rest and sleep should be en-

603. Line 8 *read*:

of spirits may be given during the night **and repeated in one, two, or three hours if necessary.**

Line 24 *read*:

of tartar lemonade or **the ammonium citrate solution** in an alkaline aërated water may be more acceptable

604. *Add* after table:

Aquæ distillatæ 1.00 Solve.

Signa. To be given in one hypodermic injection, and may be repeated every four or five hours.

. 606. Line 19 add after "rest." :

Forchheimer considered hyosein as having a special value in cases characterized by great motor excitability.

607. Lines 1-3 *read* :

large sponge, is dashed over the body back and front for several minutes, **and as it is dashed on the body**, strong rubbing, especially of the extremities, is kept up. The patient is then dried with a rough towel, the

608. Line 18 *add* after "paresis." :

Sceleth and Beifield state that in their experience in the Chicago House of Correction Hospital this condition of wet brain or comatose delirium tremens occurred in about ten per cent. of their cases. This in our opinion must be regarded as an unusually high percentage. They regard the degree in which muscular rigidity and hyperesthesia are present as indicative of the severity of the particular case. Dana states that when stiffness of the neck becomes marked the outlook is hopeless. The condition calls for cardiac and vasomotor stimulation. Nutrition must be maintained by all practicable methods. Recovery may take place after an illness of some weeks' duration, but convalescence is always very slow.

Lines 22-23 *read* :

arise of a subacute delirium in which hallucinations **occur most frequently in connection with the sense of hearing**, but occasionally in connection with the visual, tactile and olfactory sensations. **These hallucinations may be accompanied by delusions of persecution**, but otherwise there is little clouding of the intellect, and consciousness and orientation are quite clear. The patients are as a rule young and well

Lines 32-35 *read* :

so that he often flies in terror from his imaginary persecutors. **In some cases bad odors are detected; in other cases all food taken tastes of poison.** The consciousness of time and environment is not clouded, and the power of connected thought and the coördination of facts are fairly normal. The hallucinations, **as a rule**, are almost wholly confined to the sense of hearing, **in contrast with those of delirium tremens in which visual hallucinations persist.** Under

610. *Add* under "References." :

Bishop, E. S. Narcotic Addiction, Jour. Am. Med. Assn., 1913, LX, p. 431.

Emerson, E. B. Alcoholism, Boston Med. and Surg. Jour., 1915, CLXXIII, p. 113.

Gordon, Alfred. Administrative and Prophylactic Measures against Alcoholism, Jour. Am. Med. Assn., 1914, LXII, p. 194.

Henderson, D. B. Treatment of Drug Addiction, Glasgow Med. Jour., LXXXV, p. 190.

- Lambert, Alex. Treatment Narcotic Addiction, Jour. Am. Med. Assn., LX, p. 1933.
- Lichtenstein. Narcotic Addiction, New York Med. Jour., 1914, C, p. 962.
- Neff, I. H. Practical Treatment of Inebriety in a State Institution, Boston Med. and Surg. Jour., 1915, CLXXIII, p. 268.
- Sceleth, C. E., and Beifield, A. T. Cerebral Edema (Wet Brain) in Chronic Alcoholism, Am. Jour. Med. Sciences, 1915, CXLIX, p. 881.
- Stearns, A. W. Delirium Tremens and Alcoholic Hallucinosi, Boston Med. and Surg. Jour., 1913, CLXIX, p. 424.

CHAPTER II

OPIUM POISONING—OPIUM AND MORPHIN ADDICTION

A. D. BLACKADER

617. Lines 1-6 *read*:

MORPHIN ADDICTION.—The morphinist is difficult to control and difficult to treat, and the symptoms of mental and physical enfeeblement appear **early**, and, as a rule, run an **early** rapid course. The introduction of the hypodermic needle by Dr.

Line 10 *add* after "use":

Diacetyl Morphin (Heroin) Addiction.—Diacetyl morphin, an artificial alkaloid, closely resembles morphin in its euphoric effects. Frequent use of the drug may induce an addiction similar to, and equally disastrous as that of morphin, and as difficult to break away from.

Line 26 *read*:

into the lining of a coat, or secreted in a slipper **or heel of boot**. The choice of the at-

620. Line 44 *read*:

which the morphin was withdrawn. This heroic, **even dangerous**, dosage fails to secure

622. Lines 35-36 *read*:

slowly, five or six of the vegetable cathartic pills (**U. S. Ph.**) are given from two to three hours after the compound cathartic

624. Line 24 (**B. F.**) *read*:

half an hour by two ounces of castor oil or a large dose of magnesium **sulphate**. Both the

CHAPTER III

PHOSPHORUS POISONING

A. D. BLACKADER

627. Lines 36-37 *read*:

jority of writers, however, recommend that it be given in **three-grain** doses every five minutes until vomiting is induced.

628. Line 3 *read*:

the yolk of eggs, must be strictly interdicted for many days **and meat of all kinds should be forbidden.** The bowels

Lines 13-16 *read*:

phorus on the heart. **In treating the secondary stage after the vomiting has subsided,** alkaline drinks should be given freely to lessen the tendency to acidosis; in severe cases, **venesection and subsequent injection of normal saline solution have been recommended.**

630. Add "Reference":

Opie, E. L., and Alford, L. B. Influence of Diet on the Tonicity of Substances Which Produce Lesions of Liver or Kidney, Jour. Am. Med. Assn., 1914, LXIII, p. 136.

CHAPTER IV

FOOD POISONING

A. D. BLACKADER AND ALBERT G. NICHOLLS

632. Line 4 *read*:

tion, chronic constipation, is harmful. The well-known **systemic**

Line 7 *add* after "bowel.":

Whipple, Stone and Bernheim have recently shown that in a closed duodenal loop a toxic substance, or substances, is formed rapidly which will give rise to symptoms of poisoning; general collapse with low temperature and a marked fall in blood pressure associated with vomiting, profuse diarrhea, and a great loss of body fluids. The cause of this perverted action of the mucous membrane is obscure, but appears to be due to the activity and enormous development of the intestinal bacteria. Symptoms resembling the above may occur in cases of simple obstruction, as well as in a definitely closed loop such as is met with in volvulus.

633. Line 11 *add* after "work.":

In considering the various forms of foodstuffs, which may give rise to systemic disorder with sometimes fatal results, we recognize, first, a small group of common foods which act as disturbing agents to normal metabolism owing to the fact that they have lost certain principles or substances which appear to be of the greatest importance in nutrition. It has recently been shown that foods contain not only proteins, carbohydrates, fats and inorganic matter in quantities sufficient to sustain nutrition by supplying energy and replacing waste, but they must also contain in certain definite amounts substances to which the name of *vitamines* has been applied by Funk. The exact nature of these *vitamines* has not yet been ascertained, but we do know that when they are defective in quantity or altogether lacking, great impairment of nutrition results, manifesting itself in a failure in normal growth in the young, and frequently in actual disease both in them and in adults. Our knowledge of these *vitamines* has been acquired chiefly by the study of the disease

known as beriberi. It was observed, clinically, that this disease was produced by the consumption of a diet consisting mainly of polished rice, and can be prevented by the use of rice from which the pericarp has not been removed. These observations were confirmed and extended by the study of analogous conditions produced artificially in birds. There is now no room for doubting that the husk of rice contains substances the absence of which induces the development of that form of neuritis known clinically as beriberi. Further, it has long been known that scurvy results from a diet which lacks some constituent of an, as yet, unknown character. It was formerly believed that vegetable salts of potash were the ingredients lacking, but the observations of Axel Holst on experimental scurvy in guinea pigs have shown that here also we are dealing with a vitamine, although a different one from that concerned in beriberi. Infantile scurvy appears also to be due to the destruction by heat of some vitamine in milk foods; a vitamine which may in great measure be replaced by the addition of orange juice or fresh beef juice to the infant's dietary. (See articles on Beriberi, Scurvy and Infantile Scurvy.)

Lines 12-16 read:

Another small group of foodstuffs may be recognized as occasionally giving rise to systemic poisoning in which particular foods, while of excellent quality and digestible and wholesome for the majority of individuals, do produce toxic symptoms in a few, owing to some personal idiosyncrasy **arising from an obscure anaphylaxis**. Eggs, veal, and even milk may

634. Line 30 read:

cheese, ice cream, and vegetables. All animal and vegetable **foodstuffs**

Line 36 read:

organized constituents into simpler organic constituents. While this is the

635. Line 26 read:

tor oil bean are also **proteins**. In 1889 Brieger and Fraenkel, working

Line 33 read:

is technically termed a *toxin*. **Unquestionably** they are, di-

636. Line 26 read:

certainly the **exact** microorganisms which lead to poisonous symptoms.

Line 30 read:

animal tissues, which, acting upon the **protein** and **nucleoprotein** of the

637. Line 11 *add* after "affected.":

The substances which produce this anaphylaxis are proteins or substances closely allied to proteins, and the hypersensitiveness is supposed to be due primarily to the action of amboceptors which break up the protein so rapidly that toxic substances are formed and liberated, and ab-

sorbed in poisonous doses. Schorer believes that in some cases a disturbance may be induced by other substances similar to those which originally gave rise to the sensitization.

638. Line 24 *read*:

dangerous. **A peculiarity of this microorganism according to Barger and Dale is that it produces a virulent toxin without obvious signs of putrefaction not only in meats but also occasionally in nitrogenous vegetable substances, such as beans and peas.** An outbreak of poisoning due to this bacillus which was care-

639. Line 1 *read*:

ham. The experimental animals which died did not exhibit **any special form of microorganism**

640. Line 37 *read*:

meat has **caused** poisoning by this organism. In one

650. Line 44 *read*:

into flour it furnished **an important** breadstuff.

656. Add under "References—Food Poisoning.":

White, J. Proceedings of the Royal Society of Medicine, March, 1913, VI, No. 6.

656. Add under "References—Opium Poisoning." (B. F.):

Lambert, Alex. Treatment of Narcotic Addiction, Jour. Am. Med. Assn., 1913, LX, p. 1933.

Rucker, S. T. Treatment of Opium or Morphin Addiction, N. Y. Med. Rec., 1915, LXXXVIII, p. 746.

CHAPTER V

PELLAGRA

EDWARD JENNER WOOD

Much progress can now be made in the treatment of pellagra because of recent advance in our knowledge of its etiology. In the beginning it must be admitted that there are still many who will not accept the idea of deficiency, but the evidence seems sufficient to the writer to justify this conclusion and to shape this chapter accordingly. The two schools of pellagrologers—the zeists and the antizeists—may now be reconciled when it is understood that corn is rendered deficient by the destruction of the germ which is the part of the grain exposed to animal and vegetable action because of its position and also because of its softness. It seems probable that the deficiency occurs equally in the wheat as in the corn, widening the causative factor of pellagra just as the case is with beriberi, which was recently shown (Little and Ohler) to have been caused by deficient wheat.

[In addition to the importance of dietary deficiency in the etiology of pellagra, intensive studies of the epidemiology of the disease have brought forward a number of other facts. Jobling and Petersen have studied the incidence of pellagra in Nashville, where the number of cases has greatly increased from 1907 to 1915. This survey included an investigation of age and sex incidence, seasonal incidence, sanitary, economic, and dietary conditions, distribution with respect to density of population and to possible previous exposure to the disease. Concerning exposure the following extract from the report is of interest:

In a discussion of the relation of a constant contact to the development of pellagra in Nashville the fact was brought out that in the case of practically 78.7 per cent. of the patients even a cursory history had revealed evidence of an association between the development of the disease and contact with previous cases. We are fully aware that in a population having a pellagra morbidity of approximately one per cent., an intimate and constant contact is bound to occur among pellagrous individuals due to purely fortuitous circumstances, not the least among these being the result of a frequent change of residence from one house

to another; and there is also the undoubted fact that, on the whole, pellagra is a disease of those economically less fortunate, who, by reason of circumstances, live together in more or less intimate contact. We nevertheless have been so impressed by the evidence that new cases develop only in those individuals who somewhere and at some time have either lived near or have associated intimately with pellagrins, that we think it might be of interest to record in graphic form some of the examples that came under observation, the more so since, with the exception of the work of the Thompson-McFadden Commission, no detailed epidemiologic studies concerning pellagra have been published in this country.

We do so fully cognizant of the undoubted value and importance of the work accomplished, which places the etiologic basis of the disease in purely metabolic disturbances due to the imperfect dietetic condition of a great mass of people. We believe nevertheless that thus far the experiments designed to elucidate this point are inconclusive and by no means final, that considerable work remains to be done both in epidemiologic studies and animal experimentation, and that for the present at least the question of etiology is still an open one.

That pellagra is a disease of certain localities, a disease of "place," has been frequently observed in Europe and in this country, and the situation in Nashville does not differ in this respect from that observed elsewhere. This grouping in certain well-defined areas in wider districts has led in theory to the correlation of the topography and the geology of the country with the distribution of the disease, giving rise, among others, to the hypothesis that pellagra is prevalent only in those regions in which lime salts are deficient in the water and silicates too abundant. The Italians emphasized also the fact that even in the larger pellagra districts more cases and more severe cases will originate in certain districts than in others, despite otherwise comparable economic and hygienic conditions.

The study of the origin and distribution of the disease in Nashville revealed numerous instances of this situation; almost all cases could be traced to their origin to some rather well-defined focal area.—EDITORS.]

Prophylaxis.—Prophylaxis is now, and will continue to be, the most important phase of the subject just as it is in scurvy and beriberi. The disease is much more cheaply prevented than cured. While a vitamin deficiency causes it the cure demands a supply of vitamin far in excess of normal requirements, and to supply this large amount to a patient with a loathing for food is often difficult indeed.

The vitamin idea, first advanced by Casimir Funk, has received fresh impetus at the hands of Goldberger and his co-workers of the Public Health Service. Certainly Goldberger produced pellagra experimentally in man by a diet deficient in vitamin and cured and prevented the disease in institutional instances. Funk suggested that the relation between pellagra and the milling of corn was the same as the relation of beriberi and the milling of rice. This work brings up the question of the relationship between beriberi, pellagra, and scurvy, which cannot be satisfactorily answered. Suffice it to say that all are deficiencies, leaving the question of the possibility of the specificity of the deficiency unsolved.

Since 1907 pellagra has been recognized in thirty states; and in the south it has become a problem second only to tuberculosis.

Corn was first connected with pellagra by the work of Marzari in

1810. The most important work along this line was that of Lombroso, who devoted twenty-five years of his life to it, and who, just prior to his death, expressed satisfaction at having reduced the disease in Italy. As a result of this work the attention of the Italian Government was directed to the inspection of corn. It was demonstrated that the imperfect covering of the embryo, together with the large amount of fat contained in the kernel, favored deterioration and rendered corn more perishable than any other form of food grains. Lombroso concluded that the disease was an intoxication resulting from the products of the life processes of certain molds, which in themselves were not harmful. He emphasized the part played by moisture, and thought that transportation, especially by water, was a cause of a great part of the deterioration. Acting on Lombroso's suggestions the Italian Government undertook the drying of corn by various artificial means. The people were taught to leave the corn on the stalk until mature, and to thoroughly dry it before storing. It is claimed by some authorities that the improvement in corn culture and more careful storing have wiped out pellagra from certain sections of Italy. On the other hand, recent reports are not altogether confirmatory of this opinion.

Ceni taught that the *Aspergillus fumigatus* and the *Aspergillus flavescens* were the direct cause, and that both of these molds were found in diseased corn. Tizzoni attributed it to a specific microörganism which he isolated from the blood, the feces, cerebrospinal fluid, and organs at autopsy. There is not sufficient evidence from these experiments to establish the claim. In spite of the fact that, in the hands of such competent observers as Lombroso, Tizzoni, Cuboni, Ceni and many others, certain changes were produced in the lower animals—as the falling out of feathers in fowl and of hair in rabbits—we are ignorant about the appearance of pellagra experimentally produced except in man, as was recently done by Goldberger. The writer has produced a condition in pigeons which is characterized by erythema of the legs. This condition is caused by feeding a deficient corn product which is not so deficient as to produce polyneuritis gallinarum. The condition is promptly relieved by feeding whole corn or the offal of the corn mill which is known commercially as corn chops.

Until recently it has been difficult to find an explanation for the appearance, in 1905, throughout the southern states of a disease hitherto unknown in that section. Certainly at that time there was no reason to attach the cause to corn, as this particular crop had been materially improved during the preceding decade. It is now recognized that several factors entered into the causation of this remarkable occurrence. It is now known that heating to 120° C. will destroy the vitamin of corn, and it is not improbable that much corn brought into the southern states from the western corn sections undergoes heating in transit. Again, in many

parts of the South, notably in those states where steam milling of corn is prevalent, the germ is removed in the process of milling and it is a proven point that this germ contains the vitamin. The appearance of pellagra in a section is often coincidental with the disappearance of the old water mill which grinds the grain *in toto*. Voegtlin and his co-workers recently showed that the use of soda and baking powder in the preparation of bread without sour milk is a common practice in the South, especially among the pellagra class. The heat of cooking liberates carbon dioxide, leaving behind the very alkaline sodium carbonate which is most destructive of vitamin. This is a most important contribution to the study of the disease. The writer was unable to produce polyneuritis gallinarum in pigeons fed for ninety days on deficient grain, but when corn bread made with soda was substituted for the raw meal the disease developed in fourteen days. This condition was immediately relieved by the administration of an extract of corn chops made after the general plan suggested by Vedder for the extraction of rice polishings. It is reasonable to conclude from clinical experience and animal experiment that there is also a causative factor in deficient wheat flour, and it is very probable that the recent practice of eating bread made of so-called "self-rising flour" is doubly harmful because the flour is too highly milled and because of the destructive action on the vitamin of the alkali.

The question is often raised as to why women and children suffer in larger proportion than men do. About this much may be said for and against an infectious process. The writer is experimenting with young pigeons and believes that he has found at least a partial explanation. Pigeons hatched from eggs of birds long kept on a deficient diet and fed continuously on this diet will develop polyneuritis gallinarum when older birds kept for many months on the same diet are able to withstand it. There seems to be no doubt that animals can be fed a diet with a gradually increasing deficiency and acquire a tolerance of some sort for it, while previously well-fed animals succumb to polyneuritis promptly. The fact that the young birds developed polyneuritis shows that they had less resistance.

TREATMENT

Many drugs have been used in the treatment of pellagra, and many mistaken claims have been made. It must be borne in mind that it is a disease of seasonal variations, and that it is a rule for improvement to occur at certain seasons regardless of treatment. From the very first of the written knowledge of the disease arsenic has been advocated. From Coletti and Perugini its use was revived by Lombroso and given new impetus. Lombroso thought that sodium chlorid was equally beneficial, but hard on the gastric digestion. As a result of this opinion measures

were adopted in Italy for the free distribution of salt among the peasantry.

Recently, as a result of the suspicion that pellagra was a disease of animal parasitic origin more nearly akin to trypanosomiasis than to ergotism, the treatment of the former was largely imitated. Babes in Roumania was the first to use atoxyl and it at once became very popular. Babes, Veseliu, and Gheorghus treated a series of cases by the combined use of arsenic trioxid and atoxyl. Simultaneously they gave hypodermically 0.5 gram ($7\frac{1}{2}$ grains) of atoxyl, an inunction of 5.0 grams (75 grains) of a one to fifty preparation of arsenic trioxid in lanolin, and 0.0013 gram (1-50 grain) of arsenic by mouth three times a day. This treatment was repeated at varying intervals, depending on the severity of the attack. The results were claimed to have been satisfactory. The writer tried this plan several years ago and was enthusiastic about it for a time, but the improvement was only temporary at best, and the patients, returning to their old manners of life, continue to have recurrences. It was the writer's custom five years ago to give from 0.33 to 0.50 gram (5 to $7\frac{1}{2}$ grains) of atoxyl every fourth day, gradually lengthening the interval between doses. After the experience of these years and after seeing impairment of vision and a great many cases of distressing multiple neuritis we have practically abandoned arsenic and feel constrained to sound a note of alarm at the tendency to give these huge doses. We have seen many cases of neuritis which were probably due to the arsenic and not to the pellagra. It is true that there is occurring in the South, at this time, a form of neuritis much like, if not identical with beriberi, which often in the writer's experience complicates pellagra. This state of things has resulted in a great deal of diagnostic difficulty. It would seem that the results of atoxyl are so comparatively trifling in the treatment of pellagra and the tendency to painful neuritis is so great that we might do well to give up arsenic entirely.

The autoserotherapy recently suggested by E. E. Palmer and W. L. Secor has been very successful in the treatment of a number of cases under the writer's observation. These observers suggested the use of fly blisters and the removal by hypodermic of the serum with immediate injection subcutaneously. They give a word of caution against the too large and too frequent dosage. The writer has thought that at times he has seen ill results attend the treatment when this warning was ignored, but, on the other hand, he has seen his colleagues give the dose every day and give as much serum as could be procured with no untoward effect. The treatment has the same limitation as drug treatment: a resumption of faulty diet causes a repetition of the whole disease process and this may occur many times in one year.

Diet, then, is the treatment. If the diet is correct pellagra will never occur. Those cases among the well-to-do occur in individuals of abnormal

appetites and tastes. The writer has under his care a young woman in good circumstances who admitted that she would never eat eggs, meat, milk, and in fact any food with a high vitamin content. Change of diet has brought about an immediate cure which will last until she returns to her vicarious manner of life. Goldberger has emphasized the importance of not considering what the family has to eat but what the patient actually eats. We often hear the report that a correction of the diet did not benefit the patient. It must be remembered that structural change cannot be undone by correcting the errors of diet. The source of trouble may be stopped and the organism given a chance for recuperation, but that is all. It must be remembered, too, that the deficiency of long standing will not be made up by a perfectly balanced diet, but that it becomes necessary to give the necessary vitamin in great excess. The patient usually has a well-defined loathing for food and will not willingly take enough of any food. The writer finds it necessary in his hospital work to use force in order to get the prescribed food taken. One patient was fed by the tube for several weeks and the result was most encouraging, though the final result was death.

Goldberger's diet of milk, eggs, fresh lean meat and legumes will prevent pellagra and will certainly cure an ordinary case. But when the case is grave or far advanced the results have not been as encouraging as the principle deserves. This is largely due to the difficulty of making the patient eat. Besides the characteristic anorexia there is also a stomatitis and esophagitis which adds to the distress.

Phosphorus pentoxid has been used as an index of vitamin in the rice-beriberi experiments and we have found it equally helpful in our experimental work. The offal of the corn mill is known commercially as corn chops. It contains 1.15 per cent. P_2O_5 while the whole grain ground without bolting contains 0.78 per cent., and Ohio meal bought on the open market by our investigation showed only 0.29 per cent. Wheat middlings, which is the offal of the wheat, contained 0.98 per cent. P_2O_5 . It is obvious that the corn chops is much to be preferred. The analysis shows it to be a splendid food, containing much more fat than good corn meal. It is made into bread without soda or baking powder and baked; mush or a gruel is also made. It is desirable to avoid long cooking and high degrees of heat.

In one instance an old white man was admitted to the ward on Tuesday afternoon. On Wednesday he was placed on an exclusive diet of corn chops, allowing him butter only in addition. No drugs were given. On Sunday he left the hospital with all symptoms entirely relieved and has had no recurrence after two months. This patient had suffered a diarrhea for several months. Two days after the treatment began he was constipated. The erythema cleared up as if by magic and the mild stomatitis also promptly disappeared.

A second case was admitted and the same plan of treatment tried. The patient had a bullous erythema, stomatitis and diarrhea. In addition to this

disease he had diabetes. After four days the pellagra disappeared entirely and a little later the patient was put on the Allen fast and did well, without any recurrence of the pellagra.

An old negro in the last stages of the disease, with marked mental change, a diarrhea which extended throughout the year, marked skin lesions and stomatitis, failed to recover under this treatment. While the distressing symptoms of the mouth and skin were relieved, the diarrhea continued and he finally succumbed.

A negro woman, about 30 years of age, having involuntary evacuations of bowel and bladder, advanced dementia, extreme skin lesions and stomatitis, was fed through the stomach tube three times in twenty-four hours. At each feeding she was given one pint of milk, three eggs and four ounces of a wheat middlings gruel. Owing to the nature of the corn chops it was impossible to give it through the tube; hence the necessity of using the wheat preparation. The patient did very well in every way except mentally. The diarrhea was greatly improved and the skin and mouth symptoms cleared up. She died suddenly of an unexplained cause.

The two unsuccessful cases are mentioned in fairness and also to show the importance of treatment before organic change takes a firm hold. A correction of diet will arrest rickets but it will not cure the bowed legs. With the exception of these two cases we have had no deaths under the present plan of treatment in about one hundred instances. In some cases the patient has failed to coöperate and the results have been in accordance. In some cases the patient has been relieved and has returned as "the dog to his own vomit and the sow that was washed to her wallowing in the mire." The results have been notably more prompt when the high grain vitamin food was taken than when the diet was of meat, milk and eggs. Often after noting a very gradual improvement on this latter diet we have added the high vitamin food and have seen striking improvement at once. Probably the best index of the efficacy of the treatment is the prompt relief of the long continued diarrhea, and in its place constipation, making a very striking contrast. It is to be further noted that the patients responded promptly when all other food was withheld. It is not desirable, however, to continue this plan for more than three days. It is to be carefully noted that corn chops must be freshly milled. Experimentation revealed the fact that the substance in which lies the virtue is most unstable and the product must be fresh every few days.

Recently P. Modinos suggested that pellagra was due to a disturbance of the adrenals through a "sympathetic syndrome." P. F. Morse found changes of an inflammatory nature in the thyroid and adrenal. The lesion of the thyroid was a chronic productive interstitial thyroiditis with compensatory reaction of the thyroid follicles. Small areas were also found of round cell infiltration in the adrenals, liver, lung, bladder, tongue, rectum and skin. This observer concludes with the statement that he regards the changes in the nervous system to be of toxic or nutritional origin. Modinos gave adrenalin in various forms and claimed good

results from its use. We have had no experience with this idea, but in one group of patients we are now adding to the high vitamin feeding two hypodermic injections daily of the drug.

Professor Isadore Dyer recommends one-half to one ounce of gelatin daily, together with the juice of two or more oranges or lemons. He prefers a diet of eggs, milk and well-cooked vegetables. In addition he gives quinin hydrobromate in three-grain doses three times a day.

Hydrotherapy has been advocated by many writers in the treatment of pellagra. All forms of baths have been tried. Such treatment should only be given under expert supervision as otherwise it is calculated to do much harm, owing to the debility of this class of cases. Cold baths especially should be used with discretion. Medicated baths, chiefly with sulphur and arsenic, have been tried. The special indication in this form of treatment is in certain skin conditions and also in intestinal disorders, especially when accompanied with marked wasting. The salt rub is also favored by some, and is particularly advised in the treatment of children.

Radical changes of scene and climate are often of the greatest benefit. It is no uncommon thing for severe cases to improve greatly, if not recover entirely, following this change and without other treatment.

Institutional care of pellagra can do no more than correct the dietary error, except in those cases in which serious mental change has already taken place. To-day we seldom see epiphyseal separation in scurvy because the diagnosis is made and treatment instituted before this stage is reached; so in pellagra it is only a short time before the disease will not be permitted to reach the stage of mental change. Far better to spend the funds now used by state institutions for the improvement of dietetic and general hygienic conditions than to make provision for cases which can be so readily prevented.

It is to be hoped that a preparation rich in vitamin will soon be provided. A. Seidel has produced from brewers' yeast, by the use of Lloyd's reagent, a concentrated vitamin which has proven very effective in polyneuritis gallinarum, but we have had no opportunity to use it in pellagra. Until some better plan is found the writer's method of feeding the cortical portions of wheat and corn will be continued. With this food will be added milk, lean meat, eggs and legumes; when procurable, corn chops prepared with as little heat as possible will be made the chief food. Good corn bread may be made of it, but the caution to avoid alkaline rising agents must be carefully heeded and the product must be freshly milled.

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III. CONSTITUTIONAL DISEASES

CHAPTER I

DISEASES OF THE MUSCLES

CHARLES LYMAN GREENE

VARIOUS FORMS OF MYOSITIS

1. ACUTE POLYMYOSITIS

688. Line 24 *add* after "digestion.":

[There is now ample clinical and laboratory evidence that muscular rheumatism and most myalgias are due to infectious microorganisms. The source of the muscle infection is usually a confined focal infection of the tonsils, sinuses, jaws, pelvic organs, appendix and gall-bladder. The myositis may be acute, chronic, local or general and may occur alone or with arthritis.—EDITOR B.]

Line 37 *read*:

Treatment.—[The primary indication is to remove the etiologically related focal infection.—EDITOR B.] Myalgias are oftentimes suggestively responsive to anti-

CHAPTER II

GOUT

(*Podagra*)

JOSEPH H. PRATT

Definition.—Gout is a chronic disorder of purin metabolism, which results in a retention of uric acid in the body and an increase of uric acid in the blood. It is characterized clinically by recurring attacks of arthritis, associated with the deposition of sodium urate in and about the affected joints.

Uric acid was long supposed to be an intermediate product of protein metabolism, but it is known now that the purin bases are its only source. Kossel demonstrated that nucleins contain the mother substances of uric acid, and his work strongly pointed to a chemical connection between uric acid and the cell nucleus. The investigations of Emil Fischer showed the relationship of uric acid to the purin bases. All these substances have in common the purin nucleus. The simplest compound of the group Fischer called purin. This is the purin nucleus combined with hydrogen.

The addition of oxygen to purin results in the formation of hypoxanthin, xanthin, or uric acid, according to whether one, two or three atoms of oxygen are added. Uric acid is therefore tri-oxypurin.

If an atom of hydrogen in purin is replaced by an amino group (NH_2), then adenin (aminopurin) is formed. The addition to this of one atom of oxygen gives rise to guanin, which is amino-oxypurin. By the addition of methyl groups to purin the important methylpurins are formed—theobromin, theophyllin, and caffenin.

Horbaczewski observed that uric acid can be formed from nucleic acid. Increased excretion of uric acid, after feeding nucleic acid, was observed by Weintraud and other investigators. Minkowski found an increased output of uric acid after feeding hypoxanthin.

Nucleic acid and the purin bases are broken down in the body by

means of ferments. Xanthin-oxydase, which converts xanthin into uric acid, is found in man in the liver, but in no other organ.

The nucleic acids of the cell nuclei are tetranucleotids, which are made up of four mononucleotids. Each mononucleotid, like nucleic acid, contains a base, sugar and phosphoric acid. The base is either a purin base or a pyrimidin base and the sugar is a pentose or a hexose. Alkaline hydrolysis splits off the phosphoric acid, but leaves the base united to the sugar. These resulting compounds are called by Levene *nucleosids*.

Levene and Medigreceanu state that the gastric and pancreatic juices contain none of the specific ferments which split nucleic acid into the simpler bodies in the animal organism, because these juices were found to produce no change in the physical or chemical properties of nucleic acid. Thannhauser and Bommes, on the other hand, maintain that human intestinal secretion, obtained by means of a duodenal tube, converted the difficultly soluble nucleic acid of yeast into a polynucleotid that was readily dissolved in water and was dialyzable. They believe that this soluble substance is absorbed from the intestine and that deep cleavage of the nucleic acid does not occur until after it has been taken up by the tissues. They injected the two nucleosids, guanosin and adenosin, into the subcutaneous tissues of healthy men and found that 75 to 82 per cent. of these substances was excreted as uric acid.

Uricase, the ferment that destroys uric acid, is not found in any human organ. In man uric acid is not destroyed. It is the end product of purin metabolism, while in dogs, cats and other mammals it is converted into allantoin.

Sources of Uric Acid in the Urine.—It was believed for many years that uric acid was formed partly from the tissues of the body and partly from the purin substances contained in the food. The former has been called *endogenous*, the latter *exogenous* uric acid. When a person is on a purin-free diet, the daily output of uric acid is very nearly constant. The amount of the "endogenous" uric acid varies in different individuals, but it is rarely less than .3 gram or greater than .6 gram in twenty-four hours. Even on a purin-free diet the excretion from hour to hour varies greatly in the same individual. On any diet less uric acid is excreted at night than during the day. The hour at which the chief purin-rich meal is taken influences the curve of elimination.

The consumption of food containing much nucleic acid, such as sweetbreads, is followed in a healthy person by a marked increase in the amount of uric acid excretion. The increase above the endogenous level has been attributed to the direct formation of uric acid from the ingested purin bodies.

Recent studies, however, have made it seem probable that the purin contained in the food is not transformed directly into the uric acid of

the urine. Certain facts, which have thrown great doubt on the generally accepted teaching of the exogenous origin of uric acid, are:

(1) The increase in the amount of uric acid excreted is not at all proportional to the amount of purin in the food. No matter how much is fed, it is rare that the daily output of uric acid is more than one gram.

(2) The increase varies with the physical character of the ingested purin. It is much less with dry than with fresh calf's thymus.

(3) The output is as great, if not greater, after feeding a purin-free extract of thymus than when the fresh gland is given.

(4) The eating of purin-free meat and even of carbohydrates causes, within a few hours, a marked increase in uric acid excretion.

(5) The administration of drugs not at all related to the purins is followed by an increase in uric acid equal to that produced by thymus. Abl says that a hundredth part of a gram of pilocarpin can more than double the daily output of uric acid.

The increased output of uric acid, after feeding food rich in purins, may be derived from the gastric and intestinal secretions or from intestinal bacteria.

Etiology of Gout.—Although much is obscure regarding the pathogenesis of gout, certain causative factors are clearly recognized. Heredity plays an important part, especially among the rich. Physical indolence and gluttony favor its development. Probably excessive meat eating is responsible for gout, rather than overindulgence in other articles of food. The disease is certainly rare in southern Europe, where the protein of the diet is largely of vegetable origin, and it is said to be unknown in Japan. Alcohol, especially in the form of porter and heavy wines, is undoubtedly a predisposing factor. Lead favors in some way the development of gout, but is of less importance etiologically than alcohol.

Gout is a disease of mature life. It is much more common in men than in women. Kraus says that among the laboring classes in Germany there are fifty to eighty cases among males to one among females.

Factors which may excite an attack of gout vary: (1) slight trauma to a susceptible joint; (2) a meal rich in purins, especially when a gouty subject has been living for some time on a purin-free diet; (3) digestive disturbances; (4) indulgence in alcohol; (5) enforced rest;¹ (6) climatic factors seem to have an influence—at least, attacks are more frequent in the spring and fall than at other seasons.

Nature of Gout.—That uric acid is the *materia peccans* in gout is not definitely established, but the weight of evidence favors this theory.

(1) Uric acid is deposited in the inflamed tissues during the gouty inflammations, but in no other disease. In the chronic cases deposits of uric acid, sometimes of large size, are found in the ears and about the

¹One of my patients, when put to bed on account of heart failure, promptly developed a severe attack of gout.

affected joints. These are called *tophi*. On microscopic examination they are found to be composed of beautiful acicular crystals of sodium urate.

(2) The blood, in gout, usually contains uric acid in larger amounts than in health, both on a mixed diet and one free from purins.

(3) The uric acid excretion, in gout, in intervals between attacks, is usually less than in health, both on a mixed diet and on a purin-free diet.

(4) There is a retention of uric acid in gout. A day or two before an attack the uric acid secretion reaches its minimum. During the attack there is a great increase in the output. After feeding a meal rich in purins—for example, 200 grams of sweetbreads—there is in health a marked increase in the uric acid eliminated in the urine in the following forty-eight hours. In gout the excess of uric acid excreted after this meal is less than in health, and the period of increased excretion is delayed, often extending over three or four days. Twenty-four hours after the ingestion of a sweetbread meal the blood of a healthy person contains no additional uric acid, but in gout I have usually found an increase in the blood two or three days after the meal was eaten.

Umber has shown that a similar diminution and delay exist in the excretion of uric acid in gout, after uric acid is injected directly into a vein. His observations have been confirmed by McClure and myself.

Thannhauser injected nucleosids—the precursors of uric acid—into healthy men. Within twenty-four to forty-eight hours 75 to 82 per cent. of the injected substance was secreted as uric acid. In cases of mild gout the excretion of uric acid was delayed. In severe gout the injection of the same amount of the nucleosid was not followed by any increased elimination of uric acid.

(5) The feeding of large amounts of purin or the intravenous injection of uric acid has been followed by attacks of gout. Three out of four gouty persons developed an attack of gout after the injection of one gram of a nucleosid.

The state in which uric acid exists in the blood is not known. Minkowski believes that it occurs combined with nucleic acids and that the uric acid, in this form, is not demonstrable by ordinary methods. There is little support for this conjecture. Gudzent thinks that uric acid exists in the blood only as a mono-urate, in which uric acid is joined to an alkali. According to his conception, this body exists as an unstable readily soluble lactic urate, which, through intramolecular rearrangement, readily becomes changed into the much more insoluble lactic urate. Schade maintains that there is a colloidal form of uric acid which plays an important part in intermediary metabolism. His views are not accepted by other physical chemists who have investigated this subject.

Theories Regarding Gout.—Umber believes that the defective excretions of purins in gout are due to an increased affinity of the tissues for

uric acid. It has been shown that cartilage normally exhibits a striking avidity for it (Almogia, Brugsch and Citron). McClure and I injected .5 gram of uric acid into the vein of a gouty patient. Four hours later none of it had been excreted, and yet it had disappeared from the blood. Even in healthy persons, however, a large part of the uric acid injected in this way may cease to be demonstrable in the blood before it is secreted in the urine.

Garrod believed that the retention of uric acid in the body in gout was due to a defect in the kidney. Recent supporters of this view have held that the permeability of the kidney for uric acid in gout was diminished, even when other substances could be excreted freely. A similar retention of uric acid has been found in chronic alcoholism by Pollak, and in cases of chronic arthritis, clinically not gout, by myself.

The acidity of the urine in gout is within normal limits. All attempts to ascribe the deposition of urates in the tissues to diminished alkalinity of the blood have come to nothing.

The Occurrence of Gout.—The disease is more common in England than in any other country, but according to Duckworth it is decreasing. In Germany, on the other hand, it occurs more frequently now than it did in the past. Umber, in his consultation and hospital practice in Altoona and Charlottenburg, was able, in 1914, to report his observations on no less than 278 cases of gout. Brugsch, in 1913, analyzed statistics based on 180 gouty patients that had been treated in Kraus's Berlin clinic.

In America gout is relatively rare. Only 41 cases were treated in the wards of the Massachusetts General Hospital from 1821 to 1915. Among the records for the first fifty years—1821 to 1871—there are only 2 cases. In Baltimore it is more frequently seen than in Boston. Fitcher states that among 30,871 medical admissions at the Johns Hopkins Hospital there were 92 cases of gout. Recently an able physician, who has been in active practice in Massachusetts for more than thirty years, brought me a patient with typical tophaceous gout, which he said was the first case he had ever seen.

Symptomatology.—**ACUTE GOUT.**—In typical cases the victim is awakened in the middle of the night by a pain in the big toe. The pain increases in intensity until the torture is unbearable. Toward morning there is some relief from the torment. When day dawns the metatarsophalangeal joint is found to be greatly swollen, the overlying skin deep red, tense and shining. The whole joint is exquisitely tender. Throughout the day the symptoms are less intense, but the second night is one of renewed suffering. The fit of gout lasts from twelve hours to fourteen days or more, depending upon its severity. There is moderate fever; the appetite is impaired; the bowels are constipated; the urine is generally scanty and high colored. As the inflammation subsides there is itching and desquamation of the cuticle.

In only five per cent. of Garrod's cases was the great toe unaffected in the first attack. Next to the ball of the great toe, the ankle is the most common seat of the affection. The upper extremities are seldom implicated in the earlier attacks.

The interval between the first and second attack may be a year or more. As the disease progresses the attacks tend to become more frequent and to recur at a definite time of the year—usually in the spring and fall.

CHRONIC GOUT usually develops secondarily, after a patient has had repeated attacks of regular acute gout. Permanent deformities of the joints develop and the attacks of acute inflammation become less severe, but more frequent. The alterations consist of partial or complete ankylosis of the joints, or the formation of chalk stones around the articulations or other parts of the body. Many articulations may be involved. The most common site of the chalky concretions is the ear, where they may attain the size of a split pea. They are more commonly situated on the hands than on the feet. Distention of the olecranon and prepatellar bursae with sodium urate is not infrequent. These enlarged, thickened bursae are of diagnostic significance.

Complications.—Slight albuminuria and cylindruria are common, even in relatively young gouty subjects. Arteriosclerosis is apt to develop at an early age; usually it is associated with a high blood pressure, hypertrophy of the left ventricle and a beginning chronic interstitial nephritis.

Differential Diagnosis.—Gout is often confused with other forms of acute and chronic arthritis: many of the cases that I have studied had been regarded as rheumatism. In gout the small joints are chiefly affected, especially the big toe; in acute rheumatism the large joints are involved. The redness of the gouty inflammation is more vivid; the pain is more intense in gout, even when the affected part is at rest; the tenderness is greater. Usually only one joint at a time is affected in gout, while many are often simultaneously involved in rheumatism. There is more edema about the inflamed joint in gout and desquamation and itching at the end of an attack—phenomena not seen in rheumatism. Gout is not accompanied by the drenching sweats so characteristic of rheumatic fever. Gout is hereditary; rheumatism is not. Gout is rare before the age of thirty-five; acute rheumatism is rare after this age. In gout there is no tendency to endocarditis; in rheumatism endocarditis is remarkably frequent. Gout is a disease of the rich, of persons who fare sumptuously and take little exercise. Rheumatic fever is a disease of the poor, of persons who are undernourished and lead laborious lives. Gout is a disease of metabolism. Acute rheumatism is an infectious disease. The uric acid in the blood is increased in gout, but not in rheumatism. In chronic gout the radiograms of the affected joints often show characteristic alterations.

Chronic gout is distinguished from *arthritis deformans* by:

- (1) The history of acute characteristic attacks of gout.
- (2) The presence of tophi.
- (3) The characteristic clear spots, seen in the radiograph plates, in the ends of the bones near the affected joints.
- (4) The constant increase of uric acid in the blood.
- (5) The low output of uric acid when on a purin-free diet.
- (6) The fall in the uric acid curve before an acute attack, and the sharp rise early in the attack, followed by a secondary drop after the inflammation has subsided.
- (7) The increased uricemia, one to three days after a purin test meal (200 grams of thymus given to a patient who has taken a purin-free diet for four or five days).
- (8) The diminished and delayed excretion of uric acid after this meal.

Treatment.—Diet and regimen are of more importance than drugs in the treatment of gout. Experience has taught that certain things favor the development of gout and that these injurious agents should be rigidly excluded. The value of frugal and temperate living in the prevention of attacks of gout has been recognized from the earliest times. Galen affirmed that those gouty subjects who indulged in eating and drinking could not be cured. Sydenham recognized that remedies were insufficient in chronic gout unless care was taken as to diet. Cullen was fully convinced that any man who acquired early in life the constant habit of physical labor and abstinence from animal food would be saved from gout, even if he inherited a tendency to the disease.

There is a like agreement among clinical observers regarding the value of moderate and regular exercise. This was highly extolled by Thomas Sydenham, who was the first to differentiate gout from the other chronic diseases with which it had been confounded. Sydenham says:

I have often thought within myself that if any person knew a remedy, of which he wished to make a secret, equally efficacious, in gout as in most chronic diseases, with regular and steady riding on horseback, he might make a fortune.

Massage should be employed when active exercise cannot be taken. Sir William Temple said that no one need have gout who could afford a slave to rub him.

So much has been learned by clinical experience. Physiological investigations conducted by workers in many laboratories over a long period of years have at length arrived at the same conclusions as did the great English clinicians of an earlier age, whose opinions were based entirely on empirical grounds.

In the light of present knowledge of gout, which can be summed up in the words of Sir Dyce Duckworth, "Without uric acid, no gout," the

attempt is made (1) to diminish as much as possible the formation of uric acid; (2) to facilitate its elimination from the body; and (3) to prevent, if possible, its deposition in the tissues.

The assumption is made by all who prepare diets for gouty subjects, as Weintraud recently pointed out, that by restricting as much as possible the purins in the food the amount of uric acid in the body will be lessened and its excretion facilitated. I have had gouty patients, however, in whom the uric acid in the blood remained persistently high—two or three times the normal amount—in spite of the fact that for months they were on a purin-free diet.

We must be on our guard not to be unduly influenced by present-day theories, especially as recent work has thrown such doubt on the belief, so long accepted without question, in the existence of "exogenous" uric acid in the urine. My experience, however, is in accord with that of von Noorden, Umber and Brugsch that gouty patients do best on a purin-free diet. Umber, who has employed a low purin diet, in many cases for months or years, is convinced of its great value in preventing the recurrence of attacks. There is no way yet known of diminishing the purin formation in the body, except by giving the patient less purin in his food.

Purins cannot be completely excluded from the diet for any long period, because even common vegetables are not purin-free. Spinach, green peas and beans contain more than other vegetables and their use should be limited. This is not generally recognized and a meat-free diet is often supposed to be purin-free. Those animal foods are most injurious that contain the greatest amount of purin substances. These are the organs rich in cells—thymus (sweetbreads), liver and kidney. The observation has been made repeatedly that an attack of gout may follow a heavy meal of sweetbreads.

The following figures, given by Burian and Schur, show how greatly the purins vary in different foodstuffs:

100 gms.	thymus	contained	0.414	to 0.516	gms. purin N		
100	" pancreas	"	0.133	" 0.18	"	"	"
100	" fresh beef	"	0.053	" 0.07	"	"	"
100	" milk	"	0.0004	" 0.0006	"	"	"
100	" white bread	"	0.01	minimal traces	"	"	"
100	" potato	"	0.0005	to 0.0006	gms.	"	"

The effect on the uric acid excretion of eating a large amount of sweetbreads is well shown in the following chart.

This patient, who did not have gout, was on a purin-low diet, except for the sweetbread meal.

Roasted or broiled meat increases the uric acid output more than boiled meat, for the purins are extracted by boiling. Caviar is free from purin. Haddock roe, fed to one of my patients, was followed by a marked increase in the uric acid of the urine. Oysters contain purin. Nearly

all cream soups, containing a meat stock, are rich in purins. Such soups as well as bouillon should be forbidden.

The retention of uric acid varies in different cases of gout. Von Noorden and Schliep tested the tolerance for purins by determining the amount of purin in the food that could be eliminated in each case of gout;

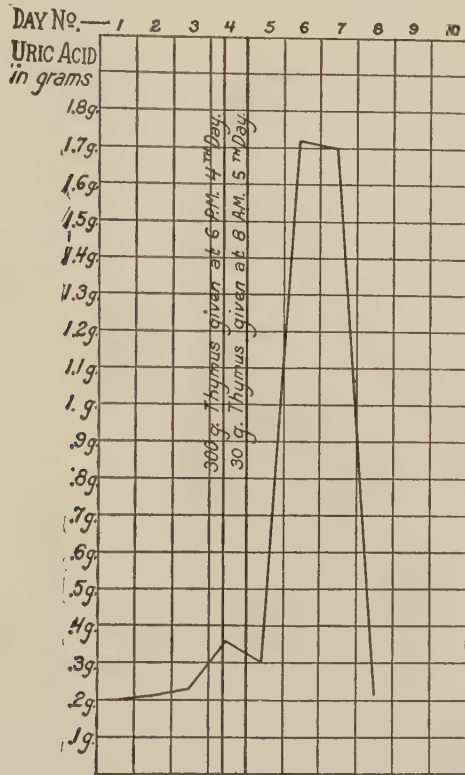


FIG. 1.—THE EFFECT ON URIC ACID EXCRETION OF FEEDING A SWEETBREAD MEAL TO A NORMAL PERSON.

then the daily allowance of meat decided upon was such that the amount of purin it contained was below the established limit of tolerance.

Umber gives a test meal, containing a definite amount of purin—usually 200 gms. of meat—to a patient who has been on a diet poor in purin. The uric acid excretion is determined daily, and the number of days required to eliminate the purin of the meal is ascertained by noting when the curve of uric acid excretion returns to the “endogenous” level. He employs purin fast days, and the number per week is determined by this test. If excretion is long delayed, there are at least four to six fast days a week, and when possible a purin-poor diet is used for months or even for years.

I have used a sweetbread test meal (150 to 300 gms. of thymus, weighed raw). Before this is fed the patient is placed on a purin-poor diet for four or five days and the uric acid output determined. Just before the sweetbreads are fed blood is drawn for a uric acid analysis. After the purin meal the purin-poor diet is resumed. The retention of uric acid in the blood is determined by making an analysis two or three days after the purin meal. There may be retention in the body when the blood shows no increase; hence it is necessary to analyze the urine as well as the blood.

There is no clear indication that proteins in the diet should be reduced. Brugsch is probably right in insisting that the purin-poor diet should not be protein-poor as well. I have given my patients an unlimited amount of milk and cheese and have not restricted the amount of vegetable proteins.

Fat and carbohydrates should be given freely, unless obesity or diabetes complicates the gout. All kinds of fresh fruits may be eaten. The use of carbohydrates in gout has been largely restricted in the past, owing to the teachings of a former generation, but without warrant on either clinical or experimental grounds. If the patients are poorly nourished, they should be given a diet rich in fats and carbohydrates. Even sweets are allowable.

Alcohol should be forbidden. Uric acid is not formed from it, but the nuclein metabolism is disturbed by its use. On a purin-free diet the administration of alcohol is said by von Noorden to be followed by an increase in the uric acid output. Pollak showed that in chronic alcoholics the excretion of "exogenous" purin was diminished and retarded.

Coffee and tea contain methyl-purins. It is probable that they can be partly demethylized in the body. Since Besser has shown that coffee can produce a rise in the uric acid output, it is advisable to use coffee that has been freed from caffein.

The patient should not abandon the purin-low diet, even if no improvement is noted, for many weeks. The change from the ordinary diet to the restricted one may be followed by an attack of gout.

After the patient has been on a purin-free diet for from three months to a year after an attack of gout the experiment may be allowed of giving meat once or twice a week at the mid-day meal. Any kind of red or white meat or fish may be chosen. The portion, if broiled or roasted, should not weigh over 100 grams. If boiled meat is selected, 150 grams may be taken. Thymus, kidney, liver, herrings and sardines should be forbidden, as they are very rich in purins. Later the number of purin days per week may be slowly increased.

PURIN-POOR DIET FOR PATIENTS WITH GOUT

- BREAKFAST:** Fresh fruit. Caffein-free coffee with cream or cocoa. Cereals with cream. One or two eggs. Bacon. Toast or rolls.
- DINNER:** Vegetable or cream soups, prepared without meat stock. Meat substitutes made with cheese, such as cheese soufflé and Welsh rarebit (Edam, Swiss and Roquefort cheeses contain less purin than American or cream cheese). Macaroni. Rice, potatoes, stewed corn, tomatoes, cauliflower, asparagus, carrots, parsnips, turnips, squash, onions, radishes, celery. Vegetable salads of all kinds; vinegar or lemon juice may be used. White bread or corn bread. Fresh or preserved fruits. Puddings made of rice, sago, tapioca, with cream or fruit sauces. Nuts. Milk.
- SUPPER:** Eggs. Rice or hominy. Buckwheat cakes with maple syrup. Salads. Crackers and cheese. Fresh or preserved fruits. Custards. White bread or toast. Milk or weak tea.

The evening meal should be simpler than that taken at mid-day. Butter should be taken freely at each meal. During the day and evening at least one and one-half liters of water should be taken, either plain, aerated, or flavored with fruit juices. The importance of drinking a large amount of fluid should be emphasized. Umber states that observations made in his clinic showed a larger excretion of uric acid in gouty patients when water was given with a meal rich in purins than when it was withheld.

DRUGS IN THE TREATMENT OF GOUT

Colchicum.—This medicine has been extolled in the treatment of gout for generations. By some of the wisest and most experienced physicians it has been regarded as a specific in gout. Garrod asserted that sometimes gouty inflammations could be diagnosed by the striking benefit obtained from this drug. One of his patients who suffered from severe attacks said that two or three hours after taking a two-dram dose of colchicum he felt himself in Paradise. As Thomas Watson says, "A patient may be in helpless agony with a tumefied red hot joint today and walking about, quite well, tomorrow."

Colchicum autumnale, or meadow saffron, was introduced as a medicine by Baron Störk, in 1763. Another species of colchicum was employed by the ancients under the name of *hermodactyl* and was held in great repute.

In this country the great value of colchicum in relieving the pain and inflammation of gout does not seem to be sufficiently recognized, and I think doses which are too small are often prescribed. A gouty patient of mine, whose father and grandfather had likewise been victims of this disease and had taken colchicum with benefit, told me that even after he had suggested the use of this drug to his physicians they did not employ it.

The best form of administering the drug is the alkaloid colchicin. I have employed Merck's preparation made into pills or tablets containing 1 mg. each. Four to six pills are given a day, usually at intervals of two hours. At the onset of a severe attack four doses may be given within two hours. The drug should then be withheld for twenty-four hours. If diarrhea develops, its use should be discontinued for one or two days. Colchicin Houdé is also highly recommended, but I have had no experience with it. It is dispensed in granules containing 1 mg. of the alkaloid. Four of these may be given during the day.

The tincture and wine of colchicum, as sold by our apothecaries, are of uncertain action. Different preparations of colchicum that I have used have seemed weak, because in large doses they failed to produce diarrhea.

The mode of action of colchicum is unknown. Purgation is not necessary in order to obtain its beneficial effect and should be avoided. Colchicum does not diminish the uric acid in the blood or cause an increased excretion of uric acid by the kidneys, and it tends to diminish rather than to increase the quantity of urine. There is no question, however, of the great benefit obtained from its use.

The toxic symptoms due to colchicum are vomiting, diarrhea, weak heart action, coldness of the extremities and great prostration.

Atophan.—In 1908 Nicolaier and Dohrn discovered that the output of uric acid could be markedly increased by the action of several quinolin compounds, especially 2-phenyl-quinolin-4-carboxylic acid, later known as atophan. This substance was described by Doebner and Giesecke as long ago as 1887. The excretion of "endogenous" uric acid may be increased one hundred to two hundred per cent. The action of the drug in gout is the same as in health. With continued administration the increased elimination is at an end in two days. It usually exerts its maximum effect in one day. The increase in the uric acid excretion may be pronounced thirty minutes after the drug is taken.

Folin and Lyman were the first to observe that the increased output of uric acid is associated with a decrease in the blood. McLester noted a drop of fifty per cent. in the uric acid of the blood three hours after the administration of three grams of atophan.

After the drug is discontinued there is a marked fall in the output of uric acid. McLester showed that this drop is accompanied by an increase in the blood. The original level in most cases is attained in two days (Fine, Chace and Bailey).

While in normal men, after the intravenous injection of uric acid, the excretion is extended over several days and is not always quantitative, in gouty patients when atophan is given at the same time there is a prompt excretion of uric acid amounting to one hundred per cent. of the amount injected (Weintraud, Frank and Bauch).

Most investigators believe that atophan increases the permeability of the kidney for uric acid, but Abl has demonstrated that a direct relation exists between the vascular tone of the splanchnic region and the output of uric acid. He maintains that atophan acts by its paralyzing effect on the splanchnic nerve. In addition, it exerts a marked local anti-phlogistic effect on the inflamed joints.

The rapidity with which atophan often checks the pain and inflammation in an attack of acute gout is remarkable; one cannot say, however, that it is more efficacious than colchicin. I give three or four grams of atophan a day for three days. It is conveniently supplied in half gram tablets. It is insoluble in water and has a bitter taste. As it sometimes irritates the stomach, it is well to add to each dose an equal amount of sodium bicarbonate and an abundance of water. If no benefit is obtained from ten grams of atophan, its use may be abandoned. The continuous administration of the drug is not advisable. In chronic gout three or four grams may be given, one or two days in the week. Atophan has its greatest field of usefulness in combating the mild but frequently recurring inflammations of chronic gout. If occasional purin days are allowed, it is a good plan to give atophan on those days.

Sometimes, when severe nephritis has complicated gout, no increase in the uric acid output has occurred after giving atophan. In these cases of so-called renal gout, after giving atophan pain in the region of the kidney has been noted, and sometimes nausea, malaise, rapid pulse and palpitation of the heart.

Occasionally an idiosyncrasy against atophan has been observed. The symptoms are diarrhea, vomiting, urticaria, headache and tinnitus.

In some cases of gout associated with renal calculus severe colic has resulted from the administration of atophan. If this complication is suspected, sodium bicarbonate should be given simultaneously with the atophan in sufficient amount to render the urine alkaline.

Atophan has frequently been used with success in the treatment of rheumatic fever, and for the relief of pain in chronic nongouty arthritis. It follows from this that its action cannot be employed as a therapeutic test in the diagnosis of gout.

Novatophan.—Novatophan is a tasteless substitute for atophan, which is said not to disturb the digestion. It is given in the same dosage as the original preparation.

Salicylates.—Salicylates are inferior to colchicum and atophan in relieving the pains of gout. Large doses are usually necessary—four to six grams a day of sodium salicylate. It has long been known that salicylates increase the output of uric acid, and it has been recently shown by Denis that, as with atophan, this increase is accompanied by a diminution in the amount of uric acid in the blood.

Alkalies.—There is no evidence that alkalies are beneficial in the

treatment of gout. Although they have been extensively used for many years, experience has failed to show their values. Sir William Roberts used alkalies in many cases in sufficient doses to keep the urine persistently alkaline, but the gouty attacks were not diminished.

It was formerly held that the administration of alkalies favored the solubility of uric acid in the body and aided its secretion. It was later shown that uric acid probably exists in the body fluids as sodium urate. The addition of sodium ions to solutions of sodium urate decreases the solubility of sodium urate. Van Loghem found in experimental studies that the deposition of sodium urate was favored by the feeding of alkalies.

In metabolism experiments it was shown that alkalies decreased the elimination of uric acid. Under the sway of false theories this was welcomed as a favorable action. At present the effort is made to increase the output of uric acid. The use of alkalies in the treatment of gout therefore cannot be endorsed, for not only does clinical experience speak with more than a doubtful voice, but theoretical considerations indicate that they are harmful.

Mineral Waters.—Mineral waters have been extensively employed. They all contain one beneficial agent which should be taken in large amount—that is, water itself. But there are exceptions even to this statement. The free use of water in gout complicated by cardiac weakness and edema may lead to serious consequences. Garrod's warning that, in some cases, the action of mineral waters is very injurious should not be forgotten. According to Osler, much of the humbuggery of the profession still lingers about mineral waters—more particularly about the so-called lithia waters.

Experiments made in Umber's clinic showed that after a meal rich in purins there was a larger excretion of uric acid when water was given freely. Carlsbad and Wiesbaden waters were more active in this respect than plain water. These observations need confirmation before they can be accepted.

The value placed on mineral waters varies with the theories held at different times regarding the disturbed metabolism in gout. Clinical experience is still the best guide, and this teaches that spa treatment exerts a favorable influence on the disease. This may be due less to the mineral constituents of the springs than to the beneficial effect of the water itself when taken in large quantity, the regulated manner of life, the change of air and scene, the pleasant surroundings, the simple enjoyments in the open air and the removal of worry and care.

Mineral waters used in the treatment of gout may be classified in five groups as follows: (1) The simple waters, or waters comparatively free from sodium salts (to this group belong Strathpepper, Scotland; Contreville, France; and Buxton, England); (2) the simple alkaline waters (Vichy, France; Neuenahr, Germany; Bedford, Pennsylvania;

and Saratoga, New York); (3) the alkaline sulphated waters (Carlsbad, Bohemia; Marienbad, Bohemia; Bedford, Pennsylvania; Greenbrier and White Sulphur, West Virginia; and Richfield Springs, New York); (4) common salt or muriated waters (Hamburg and Wiesbaden, Germany); (5) sulphur waters (Harrogate, England; and Aix-les-Bains, France).

The simple alkaline and the alkaline sulphated waters are the ones chiefly recommended for gout. The alkaline waters containing sodium chlorid (alkaline muriated) and the alkaline sulphated waters are useful in combating the complications of gout arising from disorders of the stomach, intestine, liver, kidneys and especially the lower urinary tract.

The Uric Acid Solvents.—The uric acid solvents are valueless in the treatment of gout. The list of vaunted remedies of this class includes piperazin, lysidin, lycetol, and lithium salts. One of the few mistakes made by Garrod was the introduction of lithium for the treatment of gout. Lithium, like other uric acid solvents, increases the solubility of uric acid in a test tube, but not in the human body. The use of these preparations should be condemned, not only because they are worthless, but because they give patients a false sense of security, which frequently results in a neglect of the essential dietetic measures.

PHYSICAL THERAPEUTICS

Radium Emanations.—The hope raised several years ago by His and his coworkers, that radium emanations would prove to be of great value in the treatment of gout, has not been realized. The claims of Gudzent that uric acid was destroyed or changed into a more soluble form by radium has been disproved. Fine, Chace and Bailey found that the uric acid in the blood was not decreased when radium was given by inhalations for a long period, in strengths as high as 100 Maché units per liter, nor when administered intravenously in the form of the bromid. Yet, since excellent results have been claimed by such good clinical observers as His, Umber, and Schlesinger, its use should not be abandoned without further trial.

Hydrotherapy and Thermotherapy.—Electric light baths to the entire body (5 to 15 minutes), followed by a hot circular douche or a Scotch douche, are often of benefit in chronic gout. As a rule, cold procedures are not well borne.

Exercise.—Experience has clearly shown the value of physical exercise in the treatment of gout, although physiological studies have failed to explain this beneficial action. Hirschstein has shown that the endogenous uric acid output is not increased; in fact, he found it to be decreased by exercise.

At the onset of a mild attack the patient should be permitted to keep up and about, if there is no fever. Regular exercise should be taken in

the intervals between attacks. Walking, riding, swimming, golf, snow-shoeing, mountain climbing and gardening can all be recommended.

In chronic gout harm may result if patients with eroded joints are compelled to exercise them. In severe cases exercise should not be prescribed until radiograms of the affected joints have been examined.

SURGICAL TREATMENT

The removal of tophi by operative procedure has been almost universally condemned. It is possible, however, that good results could be obtained by modern surgical methods in properly selected cases. Riedel cured two cases of podagra by removing the capsule of the metatarsophalangeal joint of the great toe.

MANAGEMENT OF AN ACUTE ATTACK

At the onset of a fit of gout or of premonitory symptoms colchicin or atophan should be given. In my experience both drugs, given in large doses, have quickly relieved the pain and inflammation. The mode of administration has already been described. As the pain is often agonizing, and can be relieved so readily by opium, its use would be advisable unless weighty objections exist against the employment of opium or its derivatives in gout. Sydenham, Cullen and Garrod were agreed that the untoward after-effects of opium in acute gout were so marked that its use was not warranted. Their arguments are not convincing, and the action of opium in gout needs to be studied anew.

The affected joint should be slightly elevated, and wrapped in dry raw cotton covered with oiled silk. The tenderness of the inflamed part can be diminished by painting the skin with an alcoholic solution of spirosal (1 part of spirosal to 2 or 3 of alcohol), or by applying spirosal in oil (1 part of spirosal, 8 parts of olive oil), or mesotan diluted with an equal volume of olive oil. Other local applications that may be tried are laudanum and water mixed in varying proportions, belladonna liniment, and lead water. Cold or wet applications are usually poorly borne and their use is deprecated.

The diet should be limited to purin-free foods that are readily digested: Toast, oatmeal porridge, boiled rice, cream of wheat, mashed potatoes, apple sauce, simple puddings with fruit sauces; milk, tea or caffeine-free coffee with milk. Water should be given freely. If the bowels are constipated, a saline purge may be taken. After the acute symptoms have subsided the bowels should be regulated by laxative foods.

The patient should be encouraged to leave his bed when the inflammation abates and to walk about, as soon as he can, with the aid of a crutch or cane. The stiffened and swollen joints should be massaged and gently exercised as soon as convalescence is established.

CHAPTER III

ARTHRITIS DEFORMANS

FRANK BILLINGS

The writer believes that the great majority of chronic joint diseases are primarily infectious. Of course the clinician will recognize the neuropathic type (Charcot joint); the static type (pes planus, sacro-iliac and lumbosacral maladies); toxic metabolic type (gout); traumatic arthritis and types of senile arthritis as noninfectious. But these noninfectious morbid joints may become infected, because of the lowered resistance of the joint tissues.

The classification of chronic arthritis based upon anatomical and clinical conditions adds confusion to the subject. In the same patient one may observe febrile and nonfebrile stages; proliferative and degenerative types of joints; peri-arthritis, synovitis, osteo-arthritis and pan-arthritis, and joints with and without deformities. These clinical and anatomical varieties serve the purpose of clinical description, but do not indicate different diseases in an etiologic sense. Probably variations of type, degree of virulence and dosage of the infectious agents on the one side and the condition of the host as to age, debility due to physical and mental exhaustion from any cause, and other factors determine the clinical and anatomical types. Still's disease may be looked upon as a precocious arthritis deformans, and yet a typical adult form of Still's disease occurs. *Malum coxae senile*, a senile monarticular osteo-arthritis usually, may occur in middle adult life from an infectious source. Rheumatoid arthritis of Garrod, villous arthritis of Goldthwait, and other types are, in my opinion, only varying forms of infectious arthritis and are at best only synonyms of other clinical and anatomical types.

I shall consider in this chapter arthritis deformans of the infectious type. Investigation has shown that strains of the streptococci, gonococci, tubercle bacilli, typhoid bacilli and spirochaeta pallida are the most common infectious causes of chronic arthritis. When other bacteria are

found in the infected tissues of chronic arthritis and myositis they may have etiologic relations to the condition, but are probably present in the tissues as a mixed infection, or purely as parasites. The deformities which occur in chronic arthritis due to these infectious agents do not differ essentially because the morbid anatomical changes which are produced in the chronic type of infection due to the streptococcus and the gonococcus are essentially the same. The mode of infection is hematogenous and usually from a focal infection. The obstruction due to endothelial proliferation or embolism in the small arteries due to the hematogenous mode of infection is practically the same. In all types of chronic infection the virulence of the invading organisms is not high; consequently the tissue reactions excited by the organisms are much less than in the more virulent type, especially of the streptococcus and gonococcus. Therefore, instead of the production of a positive chemotaxis with purulent exudates at the point of infection, as with local infections due to the streptococcus pyogenes and virulent types of gonococcus, there is in these chronic conditions a tendency to fibrinoplastic exudates in the infected tissues and an attempt to wall off an area of infection. The low virulency of the organism, the embolic mode of infection of the tissues, the resulting tissue reaction, all tend to lessen the blood supply of the infected tissue, through the partial obliteration and destruction of small blood vessels. In consequence there is a lessened blood supply and oxygenation of the tissues which results in marked malnutrition. Malnutrition leads to secondary metabolic changes in all joint structures, tendons and muscles. These changes have been well described by Nichols and Richardson as both proliferative or hypertrophic and degenerative or atrophic arthritis. Because of these morbid changes, deformities result from muscular contraction and from the changes which occur in the bones and cartilage and other structures entering into the joints. Present knowledge is in accord with Nichols and Richardson that morbid changes both proliferative and degenerative of joint tissue cannot be differentiated etiologically.

If one considers that the infection of joint tissue is hematogenous and that a sufficient dose of infectious organisms in the blood stream may reach the peri-articular tissue or deeper tissue of the joint,—that is, the end arteries in the subcapsular tissues,—or through the nutrient arteries involve the medulla of the epiphysis, one may harmonize the morbid anatomical changes which have been so clearly described by Nichols and Richardson.

The reaction set up in the tissues of the external joint structures, in the subcapsular region and in the medulla of the bone, will depend in all probability upon the virulence of the infectious microorganisms and upon the resistance of the general body structures and of the joint tissues. They may be either proliferative with virulent bacteria—especially in young or normal individuals—and necessarily the reaction will be less, or more

degenerative in kind in the joint tissues of individuals which are poor because of age, trauma and other conditions which lessen the vitality of tissue. Continued doses of infection from the focus would necessarily add to the changes described in the joint tissue. The repeated hematogenous infection destroys more blood vessels, again and again traumatizes the infected tissue and continuously lessens the oxygen supply. We now know that in chronic arthritis infectious organisms, whether streptococci or gonococci, have a relatively low virulence. Of course the degree of virulence varies and consequently the proliferative and degenerative changes especially vary in different individuals. With continued infection of the tissues malnutrition necessarily increases for the reasons named, and this necessarily leads to retrograde metabolism. Whether the retrograde metabolism is due solely to the malnutrition or whether it is also due in part to irritants in the tissues of bacterial or biochemic origin, does not in any way alter the principles outlined. Therefore, the proper understanding of chronic infectious arthritis involves an understanding of the following principles:

(1) The infection of the joints, muscles and other involved tissues with pathogenic organisms which usually are members of the streptococcus group and the gonococcus which are of relatively low virulence; (2) a hematogenous infection with endothelial proliferation and embolism with resulting injury of blood vessels and small hemorrhages into the infected tissues; (3) lessened blood supply, poor oxygenation, consequent relative starvation of the infected tissues dependent upon the malnutrition and poor oxygenation, all of which are favorable conditions for the continued life and multiplication of the infectious organisms, and finally (4) retrograde metabolism due to the malnutrition.

In the chronic infection due to the streptococcus, chronic arthritis may occur alone or associated with chronic myositis, and chronic myositis may also occur alone, involving single or groups of muscles. In chronic gonococcus arthritis the muscles are rarely, if ever, involved. Tenovaginitis is, however, more apt to occur in chronic gonococcus infection.

Various anatomical types of chronic infectious arthritis may occur, which doubtless depends upon the degree of bacteriemia, the degree of virulence of the infectious organisms, the resistance of the tissues and the fact that the mode of infection is hematogenous; consequently we may have a peri-arthritis, a synovitis, an osteo-arthritis or a panarthritis. Any or all of these types may exist in the same individual. The primary infection may be severe enough to simulate acute rheumatic fever or mild rheumatic fever. Usually the disease begins insidiously, but there may be in many patients periods of increase in temperature usually of a febrile type. There is always a great deal of soreness of the infected tissues, which is aggravated by anything which disturbs the general or local circulation, as chilling the body, fatigue and general nervous irritability.

Because of the varying degrees of activity of the focus there may be reinfection from time to time of the joints, muscles and other tissues, with consequent aggravation of the symptoms. Usually there is but little pain excepting with exercise of the involved organs. Chronic gonorrheal arthritis is more apt to involve the intervertebral joints and ligaments, the sacro-iliac, sternoclavicular and temporomaxillary joints than the streptococcus, but inasmuch as the streptococcus may also infect the four named joints, involvement of them does not necessarily indicate a gonococcus infection. Chronic infectious myositis, which may occur as a part of the chronic streptococcus arthritis, or alone, is associated with shortening of the muscle bundles due to the embolic infection, with subsequent hemorrhage and connective tissue proliferation. At the time of infection there is usually tenderness and pain when an attempt is made to contract the muscles. When at rest there is usually no discomfort. There is apparently an elective affinity of the infectious organism for certain muscles, notably the masseters, the biceps humeris, the hamstrings, the anterior tibial and erector spinal muscles. Other muscles are sometimes involved and in some instances practically all skeletal muscles are included in the infection. In all of these chronic types of arthritis and myositis there may be general debility with anemia, emaciation and nervous irritability due to the long continued infection. Often these general conditions are aggravated by methods of treatment, in starvation diets and purges which weaken the patient, and by the over-use of drugs. In recent years the irrational use of vaccines and of toxic extracts of bacteria has added to the miserable condition of the patients.

These general weakening influences add to the conditions which promote retrograde metabolism in the infected tissues, so that in all patients who present the worst type of the condition there is a tendency to such a degree of retrograde metabolism that the connective tissue group comprising aponeurosis, tendons and cartilage is changed partially or wholly into bone.

Treatment.—In the treatment the primary necessity is to obtain a knowledge of the patient's general condition and to locate existing foci of infection. The result of rational management will depend partly, in any event, upon the degree and character of the morbid tissue changes in the joints and muscles, upon the command one may have in the management and upon the age of the patient. Destructive lesions of bones and cartilage, bony ankylosis, extensive sclerotic changes and atrophy of muscles cannot be repaired. Indeed because of the destruction of blood vessels and the resulting want of nutrition, continued retrograde metabolism favors the change of the connective tissue group, tendons, aponeurosis, ligament and cartilage into bone. This is true of all types of chronic infectious nonpurulent arthritis of whatever bacterial type. Therefore, if the treatment is to result in the arrest of the disease with advanced

morbid anatomical changes or in the recovery of those with nondestructive morbid tissue changes, institutional care is required to insure the necessary command of the patient over a sufficiently long period of time to remove all focal sources of infection, to build up general nutrition and to restore as nearly as possible the blood circulation in the infected tissues. This method of management is necessary to stop the sources of systemic infection, to build up the body defenses against the existing systemic infection, to improve the general and local nutrition as the chief means of arresting retrograde metabolism and at the same time to promote resolution of the morbid infectious processes. Rationally the younger the patient the readier will be the response to the management.

In the preliminary general management one may need the aid of qualified specialists in the examination of the nasopharynx, ears, accessory sinuses, pelvic organs and blood, and Röntgen films of jaws and plates of joints to locate etiologic infectious foci and to determine the degree of the joint changes. Microscopic examination and cultures of blood, accessible exudates of joints and of foci in the head, pelvis and elsewhere and of the urine and feces may give valuable information of the character of the bacterial infection. With the consent of the patient always, a harmless and, under local anesthesia, painless removal of pieces of infected muscle, joint capsule, fibrous nodes and lymph nodes proximal to the infected tissues enables one to study the morbid histology and with a proper technic to isolate the causative infectious microorganisms from the tissues. But important as the study of the exudates, tissues and bacteria may be, the real and important principle is to know all that one may of the physical condition of the patient. Following this diagnosis, the management includes:

1. The removal of all primary and, if necessary, all secondary foci of infection. To make sure that all sources of focal infection have been obliterated, repeated examination should be made. Buried tonsillar tissue may be left at the primary tonsillectomy. An infected sinus may not have been adequately treated. Alveolar abscess may finally require the extraction of the tooth. An apparently cured gonococcus infection of the prostate and seminal vesicles may recur. Constant vigilance is necessary to insure the abolition of continued systemic reinfection.

2. The building up of the natural defenses of the body. To accomplish this involves close attention to important principles, including mental and physical rest, nourishing food, restorative tonics when indicated, cheerful environment, good air and sunshine and with some patients the use of suitable bacterial antigens as vaccines to stimulate the formation of specific antibodies in the tissues of the patient. Mental and physical rest must be rationally supervised to meet the idiosyncrasies of the individual. Isolation and continuous bed confinement may be exchanged for open ward and partial chair treatment to meet the viewpoint of the

patient and thus promote the most efficient rest of mind and body. This absolute rest must be maintained until in febrile cases all fever shall have disappeared and also until the severe soreness of the joints and muscles aggravated by motion shall have diminished, for until then the exercise of infected tissues lowers the natural resistance and thereby increases the morbid process of the joints and muscles. Often the temporary application of restraining bandages, splints and casts may favor the diminution of the local infection. The usually poor general nutrition of patients with chronic infectious arthritis calls for a generous mixed diet including an abundance of fats, oils, green vegetables and fruits. The emaciated tissues demand a full allowance of protein-containing food, both animal and vegetable. A plentiful amount of water, milk, buttermilk, cream and fruit juices must be taken. When necessary, hematinic and other tonics and laxative and simple analgesic palliatives, such as the salicylic acid compounds, may be judiciously given. There are no specific drugs to be used and narcotics should be avoided in these chronic diseases.

The mental depression of this class of patients retards improvement; hence the need of a constant, cheerful environment and an optimistic attitude of all who come in contact with them.

With the sources of systemic infection obliterated, and the existing systemic infection diminished or entirely controlled by the management described, other measures must be added to the treatment which may stop further retrograde metabolism and in favorable conditions may result in the restoration of normal anatomical and functional conditions of the tissues of the joints and muscles. These measures are so important that the failure to apply them adequately means failure in the whole management. The object of their use is to attempt to restore nutrition to the starved tissues of joints and muscles which have been deprived more or less of blood and oxygen by the embolic mode of repeated infection from the primary focus, for as long as the infected tissues are starved, conditions exist which are favorable to continued infection, and, furthermore, local malnutrition leads to retrograde metabolism.

In addition to the measures already advised to increase the general nutrition, the local malnutrition may be wholly or partly overcome by an improvement of the general and local blood circulation. The measures consist of hydrotherapy, active and passive exercise, local application of superheated dry air and the Bier blood congestion method by the application of the rubber bandage.

Hydrotherapy in the form of alternating hot and cold shower or spray baths, applied daily for a few minutes, flushes the blood to all the parts of the body without fatigue to the patient. If the force with which the water strikes the body is relatively high, the improvement of the circulation is greater. The tonic effect upon the circulatory organs of

the application of cold water to the skin is well known. A cold plunge bath is disagreeable to these enervated patients. The alternating hot-cold spray repeated several times in a few minutes is borne without complaint, and the result is quite as good as the use of the cold bath alone. In the absence of facilities for applying shower or spray baths, salt glows and alcohol rubs may be utilized as poor substitutes of the cold bath.

Passive exercise of joints and muscles may be given by nurses or more efficiently by individuals trained to give massage. Mechanical aids in the form of the Zander apparatus, if rationally used, give good results. Active calisthenic exercises may be so taught that under proper supervision each patient will have the benefit of periods of exercise modified to meet individual conditions. Other active exercise, like walking, riding, driving, swimming and gymnastic work, may be taken up at the proper time. An individual qualified by education and experience should have the supervision of the treatment by baths and mechanotherapy.

Chronic arthritis due to *syphilis* may be recognized from the history and by Wassermann blood serum test. The proper application of salvarsan, mercury and the iodids in addition to hygienic and mechanotherapy will afford great relief. Spondylitis deformans requires the attention of the orthopedic surgeon in addition to the general management outlined above. *Static* types of arthritis require proper exercises and apparatus to overcome the faulty postures and displacement of organs and bones.

VACCINATION IN ARTHRITIS

For a period of years the writer used autogenous vaccines in the treatment of arthritis. The cultures of the bacteria used were made from confined infections about the mouth, throat, nose and other sites. Subcultures were made of dominant colonies of bacteria grown on blood agar and other solid mediums. Mono- and polyvalent vaccines were made of dominant streptococcus strains. In some instances the vaccines were made from strains isolated from human tissues, after animal passage. Some vaccines were sensitized with antiserum obtained by inoculating a horse with strains of streptococci obtained from the infected tissues of arthritic patients. These autogenous vaccines were used hypodermically every five to seven days in the dose of 100,000,000 to 2,000,000,000 or more. In a few patients daily vaccination was practiced experimentally. The local, focal and general reaction following vaccination was carefully observed. Local reaction in the form of circumscribed redness, elevation of skin and some tenderness usually occurred in the first three or four injections. With continued use slight tenderness was the only local effect. General reaction evinced by rise of temperature and general body discomfort was practically absent. Focal reaction manifested by objective evidence of disturbance of joint tissues did not occur. Some patients

expressed the opinion that the vaccinations were followed by less discomfort, while others complained of more pain. The opsonic index was estimated painstakingly, before and after vaccination. It was used as nearly as possible as a guide to vaccine dosage and time of revaccination for many patients over a long period of time. Two hundred and seventy-five patients received vaccines. Two hundred and fifty received no vaccines. All received the general management outlined above. The result of the management was quite as good in the unvaccinated as in those who received the vaccine. The general management, detailed above, includes the important factors, and all of these must be faithfully carried out.

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CHAPTER IV

DIABETES MELLITUS

DAVID RIESMAN

Diabetes was known to the ancients as a disease characterized by thirst, excessive urine, and wasting of the flesh. Aretæus the Cappadocian gives a remarkable description of it in the following words: "The nature of the disease, then, is chronic, and it takes a long period to form; but the patient is short-lived, if the constitution of the disease be completely established; for the melting is rapid; the death speedy. Moreover, life is disgusting and painful; thirst unquenchable; excessive drinking, which, however, is disproportionate to the larger quantity of urine, for more urine is passed; and one cannot stop them either from drinking or making water. Or, if for a time they abstain from drinking, their mouth becomes parched and their body dry; the viscera seem as if scorched up; they are affected with nausea, restlessness, and a burning thirst; and at no distant term they expire." He derives the word diabetes from *διαβήτης*, a siphon, an etymology not accepted by all authorities. The credit for having discovered the sweet character of the urine belongs to the English physician, Thomas Willis, who says: "The statements of many authors, that the liquid imbibed is excreted little, if at all, changed, is very far from the truth; for in every case which I have met, and I believe that this holds true for all cases, the urine has differed greatly from the imbibed fluids, as also from any humor which is wont to be generated in our bodies, in that it is remarkably sweet, like a solution of honey or sugar." (Quoted by A. E. Garrod.) A hundred years later Matthew Dobson and the apothecary Poole isolated the sugar from diabetic urine, Dobson at the same time showing that such urine undergoes a vinous and acetic fermentation. Finding that the blood serum of the diabetic patient tasted sweet, he concluded that the sugar in the urine came from the blood and was not made by the kidneys. This shrewd surmise stamps him as the discoverer of hyperglycemia. Chevreul in

1807 determined the sugar to be glucose or dextrose. John Rollo was the first to lay down the principles of dietetic treatment. Since then history has been made so fast that it is useless in this article to go into details. Many facts will be brought out later. Those who are especially interested may consult the works of von Noorden, Naunyn, Lépine and other standard works.

Frequency.—Diabetes seems to be increasing in frequency. This is shown by the gradual rise in the death rate from the disease and by the greater frequency with which it is met in practice. Being, however, an unreportable affection, there are no accurate data at hand as to the actual incidence. In the following table (Bulletin No. 109, Department of Commerce and Labor, Bureau of the Census) are given the total mortality from diabetes and the death rate per 100,000 inhabitants in the registration area of the United States during the years 1906-1910:

	Total Mortality	Death Rate per 100,000 Inhabitants
1906.....	5,331	12.7
1907.....	5,801	13.5
1908.....	6,274	13.4
1909.....	7,024	13.8
1910.....	8,040	14.9

A similar increase in the mortality is noticeable in other countries, and especially in the large cities. Le Goff gives the following table of deaths from diabetes in Paris per 10,000 inhabitants:

1880.....	0.644	1895.....	1.525
1881.....	0.683	1896.....	1.504
1882.....	0.737	1897.....	1.596
1883.....	0.607	1898.....	1.580
1884.....	0.924	1899.....	1.526
1885.....	1.165	1900.....	1.700
1886.....	1.150	1901.....	1.481
1887.....	1.291	1902.....	1.462
1888.....	1.309	1903.....	1.511
1889.....	1.375	1904.....	1.601
1890.....	1.345	1905.....	1.665
1891.....	1.291	1906.....	1.760
1892.....	1.241	1907.....	1.785
1893.....	1.439	1908.....	1.704
1894.....	1.245	1909.....	1.930

It cannot be maintained that the increase in mortality is due to greater accuracy in diagnosis, for the urinary tests upon which the diagnosis is

based have not materially changed in the last twenty or thirty years. Some writers attribute the increase to the fact that the number of persons leading a sedentary life has greatly augmented and that such a mode of life is a predisposing cause of diabetes. There has also been within the last few decades a great increase in the use of sugar. Governmental statistics show that in the United States in 1822 (the first year of which there is any record) the consumption per capita was only 9 pounds—which had increased to 65 pounds in 1900, to 76 pounds in 1906, and to 85 pounds in 1915. In Japan, however, although the sugar consumption is decreasing, diabetes is on the increase. (Sei-i-kwai, October, 1916.)

Diabetes occurs among all classes of society, but is most common among the well-to-do, who eat a great deal but who do not take much physical exercise. It is, however, quite frequent in dispensary or outpatient practice, and is not rare in this country in the negro race. In Paris, as the statistics of Le Goff (*loc. cit.*) show, it is especially prevalent among lawyers, officials, professors, and physicians, a circumstance that gives color to the dictum of Montesquieu, "*Le souper tue la moitié de Paris, le dîner l'autre.*"

The Jewish race shows a special liability to diabetes. Thus von Noorden found the deaths from diabetes among the Jews of Frankfort 1.9 per cent., and among non-Jews 0.29 per cent. In this country, as far as my personal experience goes, the difference in the liability of Jews and non-Jews is not as great as it is in Germany, Austria, and Hungary.

Diabetes is rare and usually of a mild character among the Japanese and Chinese, notwithstanding that they are a rice-eating people.

Diabetes occurs in all ages and in both sexes. Under the age of ten the two sexes suffer with nearly equal frequency. Later in life the disease is much more common in the male sex. No age is exempt—diabetes has occurred in infants under one year, and is certainly not rare in early childhood. After the age of twenty-five years it increases in frequency.

Heredity plays a very large part in diabetes, and is traceable in at least 20 per cent. of all cases. The disease may occur in brothers and sisters, without existing in parents—frequently these familial cases are of a mild type, as pointed out by Salomon, Joslin, and Riesman. In a given family it often has association with obesity and gout. The occurrence of conjugal diabetes, the alleged development of diabetes among laundresses who had washed the clothing of diabetics, and a few similar facts have led some writers to consider diabetes an infectious disease. Hutinel has collected nearly all the cases bearing upon this point. The infection is supposed to enter through the alimentary canal and to pass up the duct of Wirsung, causing an ascending pancreatitis. That the pancreatitis may be infectious cannot be gainsaid, but that is no warrant for considering diabetes an infectious disease.

Etiology and Pathogenesis.—The true cause of diabetes is still

unknown. There is unquestionably a diabetic tendency, but this fact cannot, as is done by some writers, be used as an explanation of the origin of diabetes. It means no more than to say that tuberculosis, pneumonia and typhoid fever occur in those predisposed to these diseases. The essential feature of the disease is a disturbance in the carbohydrate metabolism as a result of which an excessive amount of sugar accumulates in the blood. The factors bringing about this disturbance are not definitely known. Great progress was made through von Mering and Minkowsky's brilliant discovery that complete extirpation of the pancreas in dogs is invariably followed by diabetes. The conclusion seemed warranted that the pancreas supplied an internal secretion essential to carbohydrate metabolism. Other observers, while not denying the results of pancreatectomy, attributed them to interference with the nervous mechanism, an objection that was soon decisively answered. If the pancreas is excised and a piece transplanted under the skin diabetes does not occur, despite the fact that the nerves about the pancreas suffer the same trauma (Murphy, Pratt, and Spooner). A similarly conclusive experiment was performed by MacCallum. MacCallum tied off a part of the pancreas from the rest and allowed it to undergo atrophy for a year. At this time the remainder of the pancreas was extirpated, and after a transient glycosuria the dog recovered completely. A subsequent extirpation of the film of tissue representing the atrophied part of the pancreas which had been left behind caused a most intense and persistent glycosuria. Extirpation of the pancreas is followed by the disappearance of glycogen from the liver and muscles. Support to the pancreatic theory of diabetes was given by the observations of Opie, Weichselbaum, Cecil and others that the organ most commonly diseased in diabetes is the pancreas. A variety of changes has been discovered, but whatever they are they seem to affect most frequently the islands of Langerhans. Many have therefore concluded that the islands are the source of an internal secretion necessary to the carbohydrate metabolism, the absence of the secretion giving rise to the diabetic process.¹ Cohnheim has shown that sugar cannot be broken up by pancreatic extract alone nor by muscle substance alone, but when muscle juice and pancreatic extract are together allowed to act on sugar solutions the sugar is decomposed. As heat destroys the activity of the muscle extract, but not that of the pancreas, Cohnheim concludes that the muscles contain a glycolytic ferment which requires something from the pancreas for its activation. A number of other experimenters have not confirmed these observations. The masterly work of F. M. Allen has greatly advanced our knowledge of the relation of the pancreas to diabetes. Allen in his experiments found that removal of nine-tenths of the pancreas produced in dogs a severe and rapidly

¹ Warthin and Wilson believe that latent syphilis is the chief factor in the production of the form of pancreatitis most commonly associated with diabetes.

fatal diabetes. When a somewhat larger fragment than one-tenth of pancreas was preserved, a milder type of diabetes resulted, which lasted for some months and then led to the death of the animal. When a still larger fragment was allowed to remain the dog became potentially diabetic. That is, during starvation or on a meat diet it was aglycosuric, but excreted sugar when fed on bread. When, in such an animal, the bread is replaced by meat, the sugar may disappear; but if the bread diet has been kept up too long the glycosuria becomes a permanent diabetes. With still larger pancreatic remnants, the dogs are aglycosuric on a meat or a bread diet, and maintain a fairly normal existence; but if sugar is given them glycosuria appears. By continued sugar feeding a permanent diabetes is established, a return to a meat diet failing to remove the sugar from the urine.

These researches prove that diabetes—at least in the experimental animal—is connected with insufficiency of the pancreatic function, an insufficiency that may be brought about abruptly by the removal of nine-tenths of the pancreas, or gradually by exhausting the functional power of the remainder of the organ, when a smaller portion is removed. Allen applies these facts to man, and holds that diabetes must be looked upon as *a weakness or exhaustion of the pancreatic function*.

A case reported by Jurist corresponds so closely with the observations of Allen on the dog that it almost has the value of an experiment. The patient had gangrenous pancreatitis, from which he recovered after an operation that involved the removal of a considerable part of the pancreas. He did very well for a time; subsequently, however, he developed diabetes and died in coma. He was the son of a diabetic mother.

The function that Allen assigns to the pancreas in carbohydrate metabolism is the supplying of a chemical substance, a hormone, or, as Allen calls it, an amboceptor, by means of which the sugar is able to combine with the tissue cells. The amboceptor is secreted by the islands of Langerhans. In its absence the tissues are unable to utilize the sugar that is brought to them.

Additional light has been thrown on the relation of the pancreas to diabetes by the so-called parabiosis experiments. Hédon united two dogs—one made diabetic by pancreatectomy; the other normal—by joining their carotid arteries. The glycosuria disappeared in the diabetic dog, while the normal dog showed only a transient glycosuria.

Forschbach and Pflüger also united a diabetic and a normal dog into one parabiotic double animal, with the result that the sugar and the cachexia disappeared in the diabetic dog, the condition of both animals scarcely differing from that of health.

The importance of the pancreatic hormone is strikingly shown in the interesting experiments of Knollton and Starling. By means of an ingenious device they arranged a heart-and-lung preparation in such a way

as to keep a dog's heart beating for hours. A normal heart, under such conditions, consumes a considerable amount of sugar from the circulating fluid; but the heart of a dog made diabetic by pancreatectomy, when its own blood is used, takes up practically no sugar. If, however, the heart of a diabetic dog is supplied with normal blood, it is able to consume sugar. Furthermore, when a small amount of pancreatic extract is added to the perfused diabetic blood, there is a rise in the sugar consumption of the diabetic heart. Starling believes that the conclusion is justified that normally the pancreas produces a hormone, the presence of which in the blood is essential to the assimilation and utilization of the blood sugar and that pancreatic diabetes is more likely to be caused by a diminished capacity of the tissues to make use of the sugar than by a primary exaggeration of its production.

While the pancreatic theory of diabetes, especially as formulated by Allen, is now generally accepted, mention should be made of an hypothesis originating in the Vienna School, according to which diabetes is due, not to a disturbance of the pancreas alone, but also to a disturbance of the various ductless or endocrine glands and of the liver—all known to have some influence upon carbohydrate metabolism. It has been found, for example, that glycosuria can be produced by injections of adrenalin and that this glycosuria, just like that of spontaneous diabetes, is associated with hyperglycemia. The thyroid gland and the hypophysis, and even the parathyroids, have some connection with the carbohydrate metabolism. While the details of the complicated relationship of these various glands of internal secretion to the metabolism of sugar have not all been worked out, the advocates of the pluriglandular theory of diabetes believe that the following propositions are justified: The liver and the muscles are the great storehouses of carbohydrate material in the form of glycogen. The pancreas through its internal secretion stimulates and controls the storing or warehousing of the hepatic glycogen. The suprarenal secretion has the function of liberating glycogen in response to the needs of the system, thus acting in an opposite way from the pancreas. The thyroid gland seems to possess an inhibitory influence upon the pancreas, lessening the control of the latter over the glycogen retention in the liver. This explains why in hyperthyroidism, e. g., exophthalmic goiter, glycosuria frequently occurs and why it is easily produced by the ingestion of large amounts of glucose (alimentary glycosuria). The hypophysis seems to act like the thyroid; in other words, it sends inhibitory impulses to the pancreas. The parathyroids, on the other hand, have an action opposite to that of the thyroid, an alimentary glycosuria being produced more easily after their extirpation than when they are present (Mac'Allum). The diagram in Figure 1 illustrates in a schematic way the relations just described.

It is evident that the interlocking relationship of so many organs of

carbohydrate metabolism must needs have some superior control. This is exercised by the sympathetic nervous system. The impulses pass from the floor of the fourth ventricle over the sympathetic to the left adrenal and thence through the splanchnic to the liver. If the splanchnic nerve is cut, or if the suprarenals are extirpated, puncture of the floor of the fourth ventricle (*piqûre*) is powerless to produce glycosuria.

The painstaking work of Allen, however, seems to show that whatever the part played by other glands, the pancreas behaves as if it were the dominating factor in the production of diabetes.

The *essential difference* between diabetic and nondiabetic animals—

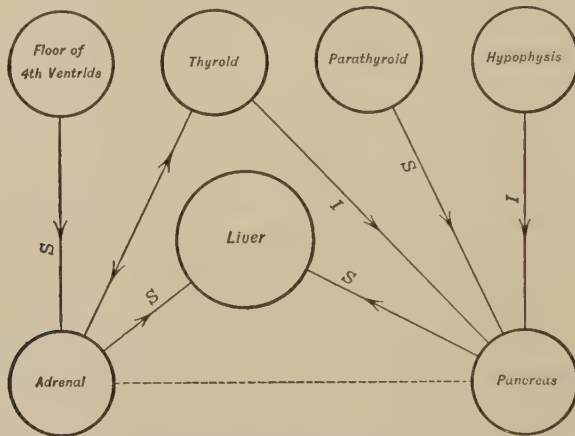


FIG. 1.—SCHEME ILLUSTRATING THE RELATION OF THE LIVER AND PANCREAS TO THE DUCTLESS GLANDS AND THE NERVOUS SYSTEM WITH REFERENCE TO CARBOHYDRATE METABOLISM.

and this no doubt is also true of human beings—is in the power to use sugar. In the normal person the power to utilize sugar usually keeps pace with the quantity absorbed. In the diabetic not only does an increase in sugar ingestion not cause an increase in utilization, but, on the contrary, it seems to tend to a lessening of the power of burning up sugar. The bearing of this fact upon treatment is at once evident.

Blood Sugar in Diabetes.—Sugar is normally present in the blood to the amount of 0.06 to 0.11 per cent. In diabetes the quantity varies from 0.16 to 1.16 per cent. or more. When the sugar exceeds a certain amount—0.17 per cent. according to Hamman and Hirschman (Eighth Annual Meeting, Society for the Advancement of Clinical Investigation, Washington, 1916), 0.149 to 0.164 according to Foster (*ibid.*) and 0.11 according to Epstein—the kidneys allow the sugar to pass through, and it appears in the urine. The amount beyond which the kidneys are not able to hold back is called the renal threshold for glucose.

Woodyatt, Sansom and Wilder, in making experiments during which they infused glucose solutions into the blood at a definite rate, found that

when 0.85 grams per kilo per hour were given sugar appeared in the urine.

Hyperglycemia is common in chronic nephritis, especially when associated with hypertension. When nephritis occurs in a diabetic the kidneys seem to hold back a larger amount of sugar, thereby raising the threshold value.

One cannot conclude, in such cases, from a diminution of sugar in the urine or from its complete disappearance, that there is a diminution or disappearance of the hyperglycemia. Thus, in the diabetic patient recently under observation, and having a moderate degree of nephritis, the urine became sugar-free. The blood, however, showed 0.22 per cent. of glucose. Myers and Bailey in a series of cases of associated diabetes and nephritis found that the blood sugar varied between 0.19 and 0.80 per cent.

The determination of the sugar in the blood is not difficult, the best methods being those of Lewis and Benedict and of Bang. (*See also* R. Fitz, Hopkins, and Epstein.) Blood-sugar estimations tell us whether, in a given case, an aglycosuric state coincides with the disappearance of hyperglycemia (Kraus). As a rule, these two go hand in hand—especially if, in the estimation of the blood sugar, the total volume of the blood is kept in mind, as suggested by Epstein. In cases of diabetes in which nephritis has developed and in which the sugar output has been lessened or entirely stopped, a determination of the blood sugar gives valuable information.

Renal Diabetes.—It is conceivable that the kidneys may become pervious to sugar when the latter is not present in excess in the blood. A few such cases have been reported and have been spoken of as renal diabetes. Strouse and Beifeld, who report a case following trauma to the head, have collected much of the literature. (*See also* Riesman.) Cases of so-called renal diabetes are distinguished from ordinary diabetes by the absence of hyperglycemia, by their mild character, and by the minimal influence of carbohydrate intake on the glycosuria. Experimentally a renal type of diabetes can be produced in lower animals by the injection of phloridzin, a glucosid obtained from the roots of certain trees, as the apple and pear. When injected into an animal phloridzin causes a glycosuria which is temporary but can be renewed by repeated injections, the animal presenting symptoms characteristic of true diabetes. As the blood shows no hyperglycemia, but rather hypoglycemia, the glycosuria must have a cause different from that operative in diabetes. Phloridzin either affects the kidneys in such a way that they become more pervious to sugar or it breaks up the hypothetic colloid combination in which the sugar, according to some authorities, exists in the blood. There is no *a priori* reason why certain substances in man might not act like phloridzin in lower animals.

The Energy Requirements in Diabetes.—As the diabetic does not properly utilize the carbohydrates and thus loses their caloric equivalent,

he has to obtain the calories lost by increased ingestion of protein and fat. Under the same external conditions the diabetic requires the same number of calories as a healthy man, namely, 35 calories per kilogram of body weight at rest, equal to 2,300 to 2,400 calories per day, and 40 calories per kilogram at work, equal to 2,800 calories. Under normal conditions these calories are obtained as follows:

100 grams protein, yielding	400 calories.
100 grams fat, yielding	900 calories.
400 grams carbohydrate, yielding	1,600 calories.

A female patient of von Noorden's ingested per day:

Proteid	148 grams	606.8 calories
Fat	1,028 grams	948.6 calories
Carbohydrates	180 grams	738.0 calories
		2,293.4 calories

At the same time she excreted in the urine 141 grams of sugar and thereby lost 578 calories, so that her food had a nutritive value of only 1,715 calories (2,293 minus 578). As the patient weighed 55 kilograms she needed 1,925 calories (55 x 35) per day, and as her food supplied her only with 1,715, there was a deficit of 210 calories to be made up by taking more of protein food and fat. Many patients lose much more carbohydrate in their urine. I have seen patients that excreted as much as 400 grams of glucose per day, or 1,600 calories. An additional loss is sustained if the patient excretes ketone bodies, since one gram of beta-oxybutyric acid yields 5 calories if it is oxidized in the body instead of being lost in the urine. These facts explain why diabetic patients have such extraordinary appetites and ingest such large amounts of food. However, after the carbohydrates are deducted, it is found that the actual calories consumed are the same as in normal individuals under the same conditions. In severe cases of diabetes, as has been shown by Benedict and Joslin, there is an increase in the metabolism of about 15 per cent. over that of normal persons. It is possible that disturbances caused by acidosis are responsible for this augmentation.

Sources of Sugar.—Normally sugar is derived from the carbohydrates, which make up a very large part of our food—in European and American countries of the temperate zone more than half of the needed calories. They are taken in a variety of forms, chiefly as starch in vegetables, such as potato, in bread and other articles made of flour; as sugar—cane-sugar, milk-sugar, glucose, levulose in fruits, and a few rarer sugars such as pentose; as dextrins, etc. No matter how introduced into

the alimentary canal, before absorption they are transformed by diastatic ferments into glucose.

The great function of the carbohydrates is to yield energy and heat. One gram through combustion liberates 4.1 calories of heat. (One calorie is the amount of heat necessary to raise the temperature of one kilogram of water 1° C.)

In diabetes the sugar found in the blood and in the urine is primarily derived from carbohydrates as long as they are ingested. In cases in which, after exclusion of carbohydrates from the diet, the sugar disappears, we may infer that the carbohydrates were the only source of the sugar. In many cases of diabetes, however, sugar continues to be eliminated after the total exclusion of sugars and starches from the food. Hence there must be other sources than ingested carbohydrates. There are but two possible ones—proteids and fats.

SUGAR FROM PROTEIN.—That sugar may be formed from protein has been proved by many experiments. There are, indeed, some proteins that contain an actual carbohydrate radicle, chiefly glucosamin. Many of the commoner proteins, however, contain no carbohydrate, yet all of them may furnish sugar. The source of the sugar in these is the amino-acid moiety of the protein molecule. One hundred grams of protein are capable of furnishing about fifty-eight grams of glucose, and as the same amount of protein gives rise to sixteen grams of nitrogen, there is a definite ratio between the glucose and the nitrogen (D:N ratio) of 3.65. Of the many amino-acids found in protein only certain ones, especially glycocoll, alanin, aspartic acid, and glutamic acid, are glucose producers; leucin, tyrosin, phenylalanin, histidin, cystin, are not—they are, on the other hand, sources of ketone bodies.

SUGAR FROM FATS.—An historically and scientifically interesting dispute has been waged over the question whether sugar is formed from fats. That fat is formed from carbohydrates is a matter of common experience, but the converse is not fully established. An animal made diabetic by pancreatectomy receiving a protein-poor diet eliminates a definite amount of sugar, that is, definite when compared with the nitrogen elimination (D:N ratio). If fat is now added to the diet no increase in sugar elimination occurs, as may be seen from the following experiments by Huebner: A diabetic patient on being fed with 176 grams of albumin and 150 grams of fat eliminated 51 grams of sugar; on adding 169 grams of fat more he eliminated 50 grams. But as Magnus-Levy points out, this is not an absolute proof of the nonformation of sugar from fat. The fat in this experiment might for the time being have been stored and thus have escaped the metabolizing process.

Fat is composed of glycerin and fatty acid. Glycerin is glycogenic, as the experiments of Külz and Lüthje prove, but, as it constitutes only about one-tenth of the fat molecule, the problem of the formation of

sugar from fat narrows itself down to the question of whether sugar can be produced from the higher fatty acids. There is no evidence that such a transformation takes place in man or animals, although it does occur in the seeds of plants.

LIPEMIA.—Normally the quantity of lipid substances in the blood plasma is rarely more than one per cent. In diabetes the amount of fat may rise to extraordinary proportions. In one case (C. Frugoni and G. Marchetti) one-fourth volume of fat was obtained by ether extraction. Sometimes the fat is present in normal amount, but the cholesterol and lecithin are much increased. It was thought at one time that a reduction of the lipolytic power of the blood was the important factor in lipemia, but more recently the condition has been ascribed to changes in adsorption.

Transient Glycosuria.—Transient glycosuria, besides being caused by the diabetic tendency, may be due to injuries, especially cerebral injuries, to febrile infectious diseases, to certain poisons, as, for example, phosphorus, arsenic, uranium, carbon monoxid, amyl nitrite, chloral, chloroform, ether, bichlorid of mercury, etc.; to the ingestion at times of thyroid preparations, to grave asphyxia, to violent emotions (Cannon, Shohl and Wright, also Folin, Denis and Smillie), and to the excessive intake of sugar. Regarding the last cause it has been found that there is a limit in practically all persons to the amount of sugar taken by the mouth that can be metabolized. If this limit is exceeded sugar will appear in the urine. Such a glycosuria is designated as *alimentary glycosuria*. There is, moreover, a personal variation among healthy individuals in their capacity for oxidizing sugar.

Von Noorden gives the following table showing the assimilation limit for various sugars; when larger amounts are ingested sugar appears in the urine:

Milk sugar.....	120	grams
Cane sugar.....	150-200	grams
Fruit sugar (levulose).....	120-150	grams
Glucose	150-180	grams
Galactose, about.....	20	grams

For starch assimilation there is in health no limit. This is probably due to the slow conversion of the starch into sugar, which enables the system to deal with it in small amounts. Every one that excretes sugar after the intake of starch must therefore be looked upon as either potentially or actually diabetic. Alimentary glycosuria lasts from four to eight hours; up to 20 per cent. of the ingested sugar may be eliminated.

In animals the tolerance for cane sugar varies greatly with the species, being highest in calves, lowest in horses (S. Iwai).

General Characteristics of Diabetic Urine.—The characteristic and

diagnostic feature of diabetes is the finding of sugar in the urine. This sugar is dextrose or glucose, a hexose or monosaccharid of the formula $C_6H_{12}O_6$. According to some authorities it is present even in normal urine, but in such minute traces—not over 0.05 per cent.—as to elude the ordinary clinical tests, the delicacy of which does not exceed 0.1 per cent. Glucose is a fermentable sugar and readily decomposes in urine through the activity of yeast cells with the evolution of CO_2 . It may happen, especially in warm weather, if but traces of sugar are present and the urine is allowed to stand for some time before being examined, that all of it is fermented and no reaction to the ordinary tests is obtained. This is a source, though not a common one, of diagnostic error.

Another cause of error is the important fact that in many cases of diabetes, especially those of mild type, sugar is not present in every specimen of urine voided. It is therefore important to examine specimens from different parts of the day, or one of a measured twenty-four-hour collection. The latter is preferable for it enables us not only to detect the sugar qualitatively, but also to calculate the total amount of sugar excreted from the percentage of sugar in the specimen submitted for examination.

The diabetic urine is pale yellow; has a high specific gravity, 1,020 to 1,060¹; and is usually voided in very large amounts. Five liters (ten pints) are common and frequently double this quantity is reached. As a rule the specific gravity does not fall with increase in the quantity of urine as is the case normally. The acidity of the urine is very marked, especially when the so-called acetone or ketone bodies are present. These bodies are beta-oxybutyric acid ($CH_3-CHOH-CH_2-COOH$), diacetic acid ($CH_3-CO-CH_2-COOH$), and acetone ($CH_3-CO-CH_3$). The other features of diabetic urine need not be discussed.

The sugar in the urine in diabetes and in most temporary glycosurias is glucose; rarely other sugars may be found. Reference has already been made to various alimentary glycosurias that may occur in otherwise healthy persons when too much of a particular sugar is ingested. The following sugars in addition to glucose may appear in the urine:

A. MILK-SUGAR OR LACTOSE.—The assimilation limit for lactose seems to be about 120 grams. Lactosuria occurs after the ingestion of amounts beyond this quantity, and also spontaneously in nursing women about the third or fourth day of lactation. The amount causing lactosuria under such circumstances is naturally much smaller than when the lactosuria is of alimentary origin. Lactose entering through the blood system, as it does in the case of puerperal lactosuria, cannot be utilized by the tissues. It can be oxidized only after it has been decomposed by

The specific gravity may, however, be low—1,008 or 1,010; sugar tests should, therefore, not be omitted by reason of low specific gravity.

the ferments of the alimentary canal into its constituents, glucose and galactose.

B. **SACCHAROSE OR CANE-SUGAR.**—The assimilation limit for this in health is large—from 150 to 200 grams. Saccharosuria is never found spontaneously in diabetes.

C. **LEVULOSE, FRUCTOSE, OR FRUIT SUGAR.**—This is found in the urine under several conditions:

- a. After excessive ingestion of it, as when inordinate quantities of sweet fruits are taken. The normal assimilation limit for levulose is from 120 to 150 grams.
- b. In diseases of the liver an alimentary levulosuria is at times easily produced by amounts below the normal assimilation limit.
- c. If diabetic urine is allowed to stand until it becomes alkaline some of the glucose may be converted into levulose.
- d. In severe cases of diabetes a spontaneous levulosuria may be at times demonstrated by proper tests, the levulose being found in conjunction with glucose. Its presence indicates that the power of glycogenesis is at a very low level. It is not impossible, however, that the alkalies that are often given in such grave cases have something to do with the development of the levulosuria.

D. **MALTOSE.**—The chief source of maltose is beer. Some persons excrete sugar after drinking beer, but whether this is glucose or maltose has not been definitely determined. A spontaneous maltosuria is said to occur at times in diabetes, but its significance is not known.

E. **PENTOSE.**—Pentose is a sugar containing five atoms of carbon. It gives the reduction tests for sugar—Nylander's and Trommer's, the latter taking place, however, only after cooling and somewhat interruptedly. The pentoses do not ferment, and as regards polarized light they show a variable behavior, some being inactive, some dextro-, some levorotatory. Three types of pentosuria may be recognized (S. Solis Cohen):

1. Alimentary pentosuria, due to the ingestion of food rich in pentoses, such as huckleberries, cherries, plums, pears, and apples, many vegetables, and wines. Milk also contains traces of pentose.
2. Complicating or diabetic pentosuria, in which pentose and hexose are eliminated together.
3. Essential pentosuria in which the excretion of pentose is persistent, independent of diet, and not associated with diabetes mellitus.

The pentose appearing in alimentary pentosuria is dextrorotatory arabinose, while in essential pentosuria an inactive arabinose is excreted. Essential pentosuria does not seem to have any deleterious influence on the

organism. Its chief interest lies in the fact that it may be confounded with diabetes and cause the patient to be denied the benefit of life insurance and perhaps to be subjected to useless antidiabetic treatment.

GLYCURONIC ACID.—Glycuronic acid is one of the intermediary products of glucose decomposition in the body. It is always found in combination with fatty or aromatic alcohols in the form of the so-called conjugate glycuronates. According to Meyer and Meyer and Neuberg an increased elimination of glycuronates precedes alimentary glycosuria and sometimes accompanies true diabetes. As the glycuronates have the power of reducing copper and bismuth in alkaline solutions their presence is likely to lead to an erroneous diagnosis of diabetes. They do not ferment. The acid itself is dextrorotatory, while the glycuronates turn polarized light to the left.

ACIDOSIS

The disturbance of metabolism in diabetes that has attracted the greatest attention recently is the so-called state of acidosis. In order to understand this condition, it is necessary to discuss briefly the factors influencing the reaction of the blood. The blood has a most wonderful power of preserving its reaction under all sorts of conditions of acid or alkaline ingestion that might tend to change it. It is especially in the neutralization of acids, whether ingested or developed within the body, that the blood possesses a remarkable reserve power resident in its alkaline bases. The reaction of the blood on the acid side is measured in terms of hydrogen ions. The test chiefly employed is that of Levy, Rowntree and Marriott which is too technical to be quoted here. The increase in the acid elements—in other words, in the hydrogen ions—of the blood causes a displacement of the CO_2 (carbon dioxid), since the latter is the weaker acid. The carbon dioxid content of the blood bears a definite relation to the carbon dioxid tension of the alveolar air. Hence, the latter may be used as a criterion of the hydrogen ion content of the blood; in other words, it is a measure of the state of acidosis. A low carbon dioxid content of the blood produced by acidosis would express itself as a low alveolar carbon dioxid tension. Methods have been devised for determining the carbon dioxid in the alveolar air, and also for directly measuring the carbon dioxid of the blood. It is impossible to describe the technic for these determinations in detail. The following methods are clinically applicable: For determining the carbon dioxid content of the blood, the method of Van Slyke (Joslin), and for determining the carbon dioxid content of the alveolar air, the method of Marriott.

It is possible that acidosis may be produced by the retention or formation of a variety of bodies of an acid nature; but at present we know little about the cause of any other acidosis than that in which the so-called

ketone acids are concerned. These ketone acids are beta-oxybutyric acid and aceto-acetic acid. They are intermediary products in the catabolism of fats; in particular, of the fatty acids with an even number of carbon atoms. If formed normally, as is probable, they are quickly destroyed; but under certain conditions,—principally diabetes,—and also in starvation, in so-called cyclic vomiting, in some of the infectious diseases, and in various states of undernutrition such as are found in malignant disease, etc., these acids are not oxidized to their end products, but accumulate in the body. They then attach themselves to the alkaline bases of the blood and tissues and drive out the carbon dioxide.

Beta-oxybutyric acid and aceto-acetic or diacetic acid are eliminated in the urine. The latter is quickly oxidized in the urine to acetone. Acetone, it is believed, is also eliminated in the breath, though Folin doubts this.

In addition to fat it is possible that protein may also be a source of ketone bodies. Some of the amino-acids, such as tyrosin, tryptophan, phenylalanin, arginin, cystin, histidin, and possibly leucin, can be shown experimentally to form fatty acids. Whether such a transformation takes place in man still remains unsettled. Taylor denies it.

The acidosis of starvation, which, like that of diabetes, is due to the ketone bodies, is quickly banished by the administration of carbohydrates. In diabetes it has been found that acidosis sometimes follows the sudden withdrawal of all carbohydrate from the diet, and that it is lessened when small amounts of carbohydrate are given and oxidized. These facts seem to make it probable that for the perfect combustion of fats in the body, carbohydrate oxidation is necessary. To quote a German writer, "The fats are burnt in the fire of the carbohydrates."

Ringer believes that normally glucose and beta-oxybutyric acid unite to form a harmless glucosid, and that failure of this union to take place is the cause of acidosis.

One of the ways that the system has of protecting itself against the harmful effects of ketone and other acids is by the formation of ammonia out of nitrogen that would otherwise go to form urea. Therefore, the determination of the ammonia content of the urine is another indirect way of measuring acidosis.

The amount of ketone bodies formed in diabetes varies. It seems to reach the greatest height in threatened or actual diabetic coma. Magnus-Levy has found as much as 160 grams of acetone bodies excreted in a single day. Some persons seem to bear acidosis better than others, and there are cases in which for weeks and months as much as 40 or 50 grams have been excreted per day without noteworthy symptoms.

Acidosis is the generally accepted cause of diabetic coma, the most serious and fatal complication arising in the course of diabetes. It is the cause of death in from 40 to 70 per cent. of all cases. Frerichs, among

400 cases of diabetes, had 250 deaths, 151 from coma. Von Noorden, among 1,853 cases, had 292 deaths, among them 169 from coma, a percentage of 57.8; Joslin's figure is 64 per cent.

Diabetic coma may occur without warning, being precipitated by nervous shock, by injury, by surgical operations under anesthesia, by an acute attack of indigestion or gastro-enteritis, and by alcoholic excesses. Diabetic gangrene and acute infectious diseases may cause a latent acidosis to pass into coma.

Coma without Acidosis.—Not every case of coma in a diabetic is the result of ketonemia. A diabetic patient may, if he has Bright's disease, develop uremic coma; and I have also seen in a diabetic patient a coma that was not uremic and in which neither diacetic acid nor acetone could be demonstrated in the urine. Similar cases have been reported by Rosenbloom.

Tests for the Acetone Bodies; Qualitative Tests.—**DIACETIC ACID.**—*Gerhardt's Test.*—Add to the urine a few drops of a strong solution of ferric chlorid. If a precipitate forms it consists of the phosphates of iron, and more ferric chlorid should be added. If diacetic acid is present a Bordeaux-red color appears. In performing this test it must be borne in mind that if the patient is taking salicylic acid or antipyrin a similar color will develop when chlorid of iron is added.

To avoid the disturbing action of the phosphates in making Gerhardt's test von Noorden recommends the following modification: 10 c.c. of a 6 per cent. solution of ferric chlorid are placed in a small beaker and the urine added, drop by drop. Even when phosphates are present in large amounts they will not disturb the reaction. The degree of intensity of the reaction is not a reliable guide to the amount of diacetic acid present.

To distinguish between diacetic acid and other substances giving the same reaction with ferric chlorid the urine should be boiled. Boiling decomposes the diacetic acid, while salicylic acid and similar compounds are not changed, and the urine continues to give the ferric chlorid reaction after boiling.

Ondrejovich's Test.—To 10 c.c. of urine acidulated with a few drops of acetic acid add 5 drops of Lugol's solution and shake with 2 c.c. chloroform. If diacetic acid is present the chloroform remains colorless, otherwise it assumes a rose color due to the dissolved free iodine. The advantages of this reaction are that it is quickly done, that it is not given by salicylic acid preparations or by antipyrin; that it does not cause a precipitation of the phosphates, and that it is very delicate. It may be used for quantitative tests; these I shall not describe in detail, but refer those interested to the original article.

ACETONE.—Add to the urine a few drops of a fresh solution of sodium nitroprussid and a few drops of glacial acetic acid, and overlay with

ammonia; following this a purple ring will appear at the junction of the two fluids.

Lieben's Test.—The urine is alkalinized with sodium or potassium hydrate; a few drops of Lugol's solution are added. If acetone is present the odor of iodoform becomes apparent and eventually crystals of iodoform are thrown down. It is better to perform this test with the distillate of the urine.

BETA-OXYBUTYRIC ACID.—There is no satisfactory qualitative test for beta-oxybutyric acid—it is estimated quantitatively by means of the polariscope (Sahli, *also* Emerson). The urine should be fermented so as to remove the dextrorotatory glucose. If the urine after fermentation turns polarized light to the left beta-oxybutyric acid is in all probability present.

PROGNOSIS

Is diabetes curable? Many with the right to speak say it is not. A diabetic is cured if he can eat like other persons without a return of glycosuria. It must be admitted that such a result is not often attained. By far the greater number of patients with diabetes, if they succeed in ridding the urine of sugar, can keep it sugar-free only by a certain amount of dietetic restriction. I am, however, of the opinion that there has been too much pessimism regarding the curability of diabetes and even regarding recovery from acidosis and coma. Diabetes in the young is rightly very much feared and certainly the majority of cases end fatally after a comparatively short time. Yet, as the following case of Huerter shows, cure is possible: The patient was a little girl of ten years with a diabetic history, though not in the immediate family. After several intestinal attacks she began to have typical signs of diabetes, with sugar up to 9 per cent. and traces of diacetic acid. Under dietetic treatment sugar disappeared and the child was able to consume 420 grams white bread without excreting sugar, and 50 grams of glucose were also without effect.

Many middle-aged and old persons with diabetes, especially if they are obese, never suffer much nor have life materially shortened by their malady. The prognosis is, however, not nearly so good if the patient is markedly arteriosclerotic.

It is probable that if cases are taken in hand early real cures may be achieved. The frequent examination of urine by the family physician, as well as the vigilance of life-insurance examiners, is sure to bring cases of diabetes under medical care much earlier than has happened in the past. This will make it possible to institute those methods of dietetic restriction by which the carbohydrate tolerance is preserved and perhaps eventually restored to the normal.

PROPHYLAXIS

In consideration of the fact that heredity plays an important part in the propagation of diabetes—one-fifth are hereditary—it is advisable to undertake some prophylactic measures in families in which the diabetic taint exists. That such measures prevent diabetes is of course beyond the possibility of proof, for one can never say in a given individual that diabetes would have developed had certain measures not been taken. Children of diabetic families must be brought up on a dietary from which sugar and candy and cakes are to a large extent excluded. If there is a tendency in the family to obesity, with or without diabetes, the life of the growing generation should be so shaped that by exercise and a rational dietary—not too much food nor too rich food—adiposity is avoided. Physicians have not hitherto entered into the field of preventive medicine with sufficient interest and purposiveness, but by taking a larger view of their function in this direction they may accomplish much in the prevention of diseases of metabolism.

Persons who, under stress and strain, or after injuries, have shown transitory glycosuria should naturally adopt a diet calculated to conserve and strengthen their carbohydrate tolerance. That is, they should limit their intake of sugars and starches. A life free from undue excitement is also important.

Prophylaxis becomes imperative in persons who have had pancreatic disease. If they have lost, either through operation or through spontaneous necrosis, part of their pancreas, they are in danger of diabetes. A proper antidiabetic regimen should be early prescribed and starches should be allowed only under constant control of the carbohydrate tolerance. Even the protein intake must be lessened. Whether the administration of fresh pancreas, as Pratt found in dogs, or pancreatic extract, has a prophylactic value remains to be investigated. With a diminishing tolerance I should feel that the use of fresh pancreas was worthy of a trial.

A measure of prophylaxis of the greatest importance and the widest applicability is frequent urine examinations. They are especially valuable in the children of diabetics and in those who have had traces of sugar. In the obese and in children of the obese and diabetic and in those with a history of previous pancreatic disease, and in all with temporary glycosuria, the urine ought to be examined at least four times a year. I am in the habit, in patients belonging to these various groups, of instituting from time to time the test for alimentary glycosuria. This test is performed as follows:

The patient provides himself with a half dozen specimen bottles bearing blank labels. On rising in the morning he takes 100 grams of glucose

and immediately voids urine into one of the bottles. Thereafter he empties his bladder every two hours, using the specimen bottles and noting the time on the label. All the bottles are then brought for examination and the urine tested qualitatively for sugar. In a normal person the glucose is all burned up and none appears in the urine.

GENERAL TABLES FOR USE IN DIETETIC TREATMENT OF DIABETES

TABLE I

Forbidden to All Diabetics

Sugar.	Gravies, sauces, and soups thickened with flour.
Candy.	Hot cakes.
Maple sugar.	Cereals.
Pies.	Rice.
Pastry.	Dried beans.
Cake.	Sweet wines.
Jelly.	Macaroni.
Preserves.	Ginger ale.
Compotes or stewed fruits.	Champagne.
Ice cream.	Liqueurs.
Syrups, molasses.	

TABLE II

Foods Usually Allowable (Modified from von Noorden)

FRESH MEATS.—All muscle of beef, veal, pork, lamb, mutton, game, either roasted, boiled, or broiled, in their juices, with butter, or with mayonnaise made without flour, either hot or cold.

VARIOUS ORGANS OF ANIMALS.—Tongue, heart, brains, sweetbreads, kidneys, marrow, calves' liver, liver of game or poultry (*pâté de foie gras*) up to 100 grams in weight.

PRESERVED MEAT.—Smoked meat, dried meat, smoked or pickled tongue, ham or bacon, corned beef, sausage (containing no bread).

Meat extracts of all kinds, meat jellies or aspics prepared from calf's foot, gelatin, and meat sauces.

FRESH FISH.—All fresh fish boiled, fried, or broiled. If the fish is fried in bread crumbs the crust must not be eaten.

PRESERVED FISH.—Dried, salted, or smoked, such as haddock, cod, herring, mackerel, flounder, sardelle, sturgeon, eels, salmon, etc. Pickled herrings, sardines in oil, mackerel in oil, anchovy, tunny fish, etc.

SHELL FISH AND CRUSTACEANS.—Oysters, clams, and other shell fish, lobsters, crabs, shrimps, turtle, etc.

EGGS.—Raw or cooked.

FISH PRODUCTS.—Caviar, roe.

FATS.—Butter, bacon, lard, suet, oleomargarin, olive oil, cod-liver oil; rich cream—one of its many uses is as a substitute for flour in preparing sauces.

CHEESE.

VEGETABLES.—Lettuce, endive, romain, cress, dandelion; celery without root, cucumbers, tomatoes, young string beans, egg plant, onions, kohlrabi (young), radishes, asparagus, Brussels sprouts, cauliflower, artichoke, spinach, cabbage, mushrooms.

Canned and preserved vegetables: canned asparagus, canned young string beans, sauerkraut, olives, pickles.

NUTS.—Walnuts, hazelnuts, almonds, cream nuts.

FRUIT.—Grape fruit, peaches, cranberries, rhubarb, green gooseberries (sweetened with saccharin).

SOUPS AND CONDIMENTS.—Meat soups and sauces in moderation.

Desserts made from eggs, cream, almonds, lemon, and gelatin, sweetened with saccharin instead of sugar.

BEVERAGES.—Carbonated waters, whiskey, brandy, light Moselle and Rhine wines, Bordeaux and Burgundy of old vintage, tea and coffee, and lemonade.

TABLE III

Foods Allowed in Restricted Quantities

CERTAIN VEGETABLES COOKED WITHOUT FLOUR AND SUGAR.—Lima beans, dry and green peas, red beets, white kohlrabi, carrots, celery root, oyster plant, potato.

FRESH FRUITS.—Apples, pears, apricots; raspberries, strawberries, currants, blackberries, huckleberries.

DRIED FRUIT.—Prunes and peaches cooked after thorough washing in water.

The following table of equivalents was prepared for me by Dr. C. B. Farr along the lines of the preceding tables but in a way better adapted to the needs of the kitchen.

TABLE IV

Table of Equivalents A

Foods containing carbohydrates, to be used only in restricted quantity, which when used entail a cutting down of the bread allowance in a proportionate amount. Modified from Janeway's and Foster's tables.

	Per Cent. Carbo- hydrates	Grams	Grams	Grams	Grams	Amount in Ounces Equal to 1 Ounce White Bread
White bread.....	51-55	10	20	30	50	1
Corn bread.....	Equiv. to 46	Equiv. to 12	Equiv. to 24	Equiv. to 35	Equiv. to 60	1 1/8
Graham bread.....	47-53	10	20	30	50	1
Gluten bread.....	47-53	13	26	39	65	1 1/8
Rolls and biscuit.....	52-60					1
Crackers, average.....	69-72					3/4
Oat cakes.....		25	50	75	125	
Wheat flour.....		8	16	24	40	
Hominy (boiled).....		20	38	50		
Rice (boiled).....		14	28	42		
Tapioca (pudding).....		15	30	45		
Macaroni (cooked).....	15.8	30	60	90		3
Spaghetti (cooked).....		30	60	90		
Cocoa (unsweetened).....		12				
Asparagus (cooked).....		175	350 ¹			
Beans, red kidney.....		25	50			
Beans, baked.....	20					2 1/2
Beans, lima.....	20	25	50			2 1/2
Beets (cooked).....		55	100			
Cabbage (raw).....		78	156			
Carrots (raw).....		60	120			
Celery (raw).....		100	200			
Corn, green (canned).....		25	50			
Cauliflower (raw).....		80	160			
Dandelion greens.....		50	100			
Egg plant (cooked).....		90	180			
Onions (boiled).....		90	180			
Peas, green (cooked).....	15	30	60	90		3
Parsnips (raw).....	13	40	80			4
Potato (boiled).....		25	50	75		
Potatoes (cooked).....	18-20					3
Oatmeal (boiled).....	11.3					5
Hominy (boiled).....	17.8					3
Rice (boiled).....	24.4					2 1/8
Milk.....	4-5					10
Apples and apricots.....	12-14					4
Apples (raw).....		35	70			
Apricots (stewed).....		40	80			
Bananas.....	22	25	50			2 1/2
Blackberries (fresh).....		35	70			
Cherries (fresh).....	15	25	50			2 1/2
Currants (fresh).....		40	80			
Grape fruit.....		200				
Gooseberries.....		75	150			
Oranges.....		30	60			
Peaches.....		50	100			
Pears.....	12-14	40	80			4
Plums.....	20	27	54			2 1/2
Prunes (stewed).....		25	50			
Raspberries.....		42	84			

¹ When no equivalent amount is given in the fourth column, it is to be understood that the amount in the third column is the maximum allowable.

TABLE IV—*Continued*

	Per Cent. Carbo- hydrates	Grams	Grams	Grams	Grams	Amount in Ounces Equal to 1 Ounce White Bread
Strawberries.....		60	120			
Huckleberries.....	16					3¼
Filberts.....	12					4½
Almonds.....	15					3½
Peanuts.....	22					2½

Table of Equivalents (Carbohydrates) B

This table shows the amounts of various carbohydrate foods which will yield 15 or 16 grams of carbohydrate, or the equivalent of a slice of bread. The composition in calories is given in round numbers. It is intended for use with the "Strict" diet to facilitate the determination of the carbohydrate tolerance.

Article	Amount	Rough Measure	Protein, Grams (Approx.)	Fat, Grams	Carbo- hydrate, Grams (approx.)	Calories	Remarks
Bread.....	30 grams	slice	2.75	.40	16	80	"Educator"
Zwieback.....	22.4 grams	1½ slices	2.00	2.00	"	97	
Soda crackers....	33 grams	11 crackers	11.00		"	110	
Macaroni (boiled)	100 grams	2 h. tbsp.	3.00	1.50	"	91	
Rice (boiled)....	66 grams	¾ tbsp.	2.00	.07	"	75	
Potato (baked)...	65 grams	½ medium	2.00	.10	"	74	Large portion 4 or 5 portions
Green peas.....	110 grams	3½ tbsp.	7.00	3.75	"	132	
Carrot.....	450 grams	12 h. tbsp.	2.00	.75	"	81	
Milk (whole)....	330 grams	1½ glasses	11.00	13.00	"	235	
Apple (raw).....	150 grams	large	.45	.45	"	72	
Grape fruit.....	150 grams	¼ large	1.00	.30	"	69	

TABLE V¹

Composition and caloric value of certain foods poor in carbohydrates, in customary portions.

100 Gm. (A Trifle over Three Ounces)	Protein	Fat	Carbo- hydrates	Caloric Value
Vegetable oil.....	1	100	...	930
Butter.....	1	85	0.5	830
Bacon (salt or smoked).....	10	76	...	748
Devonshire cream.....	2	57	0.2	538
Cream cheese (Gervais, Neufchâtel, Stilton, Stracchino, etc.).....	19	41	0.1	451
German sausage (Cervelatwurst).....	18	40	...	456
Ham.....	25	36	...	437
Cheddar cheese.....	28	33	0.2	422
Fat pork.....	14	37	...	400
Smoked ox-tongue.....	24	32	...	396
Fatty cheese (average).....	25	30	1.5	381
Yolk of egg.....	16	31	0.5	354
Fat goose.....	16	30	...	345
Fat beef and mutton.....	17	29	...	337
Brie cheese.....	19	26	0.1	320
Fresh-water eel.....	13	28	...	312
Smoked mackerel.....	19	22	...	382
Caviar.....	31	16	...	276
Cream.....	4	23	0.4	230
Fat salmon (fresh or smoked).....	22	13	...	210
Hens' eggs (weighed with the shells) (2 large)...	12	10	0.5	142

¹ From Hall (Nutrition and Dietetics, 1910, pp. 263-4).

TABLE VI¹
Carbohydrate Content of the Commoner Foods

Food Materials, as Purchased	Percentage of Carbohydrate
ANIMAL FOOD	
Beef, fresh.....	0.0
Beef, corned.....	0.0
Tongue, pickled.....	0.0
Veal.....	0.0
Mutton.....	0.0
Lamb.....	0.0
Pork, fresh.....	0.0
Pork, salted, cured and pickled.....	0.0
Poultry (chicken, fowl, goose, turkey).....	0.0
Eggs, hens'.....	0.0
Fish, fresh.....	0.0
Fish, cod, dressed.....	0.0
Fish, halibut, steaks or sections.....	0.0
Mackerel, whole.....	0.0
Perch, yellow, dressed.....	0.0
Shad, whole.....	0.0
Shad, roe.....	2.6
Sausage, Bologna.....	0.0
Butter.....	0.0
Fish, preserved (salt cod and smoked herring).....	0.0
Fish, canned (salmon and sardines).....	0.0
Oysters.....	3.3
Clams.....	5.2
Crabs.....	0.6
Lobsters.....	0.2
Sausage, pork.....	1.1
Sausage, Frankfurter.....	1.1
Soup:	
Celery, cream of.....	5.0
Beef.....	1.1
Tomato.....	5.6
Meat stew.....	5.5
Whole milk.....	5.0
Skimmed milk.....	5.1
Buttermilk.....	4.8
Condensed milk.....	54.1
Cream.....	4.5
Cheese:	
Cheddar.....	4.1
Full cream.....	2.4
VEGETABLE FOOD	
Flour, meal, etc.:	
Entire wheat flour.....	71.9
Graham flour.....	71.4
Wheat flour, patent roller process—	
High grade and medium.....	75.1
Low grade.....	71.2
Macaroni, vermicelli, etc.....	74.1
Wheat breakfast food.....	75.2
Buckwheat flour.....	77.9
Rye flour.....	78.7
Corn meal.....	75.4
Oat breakfast food.....	66.2
Rice.....	79.0
Tapioca.....	88.0
Starch.....	90.0

¹ From "Principles of Nutrition and Nutritive Value of Food." U. S. Dept. of Agriculture, W. A. Atwater, Farmers' Bulletin, No. 142, Washington, 1910.

TABLE VI—*Continued*

Food Materials, as Purchased		Percentage of Carbohydrate
VEGETABLE FOOD— <i>Continued</i>		
Bread, pastry, etc.:		
White bread.....		53.1
Brown bread.....		47.1
Graham bread.....		52.1
Whole-wheat bread.....		49.7
Rye bread.....		53.2
Cake.....		63.3
Cream crackers.....		59.7
Oyster crackers.....		70.5
Soda crackers.....		73.1
Sugars, etc.:		
Molasses.....		70.0
Candy.....		96.0
Honey.....		81.0
Sugar, granulated.....		100.0
Maple syrup.....		71.4
Vegetables:		
Cabbage.....		4.8
Celery.....		2.6
Cucumbers.....		2.6
Lettuce.....		2.5
Rhubarb.....		2.2
Spinach.....		3.2
Squash.....		4.5
Tomatoes.....		3.9
Potatoes.....		20.0
Fruits, berries, etc., fresh:		
Apples.....		10.8
Bananas.....		14.3
Grapes.....		14.4
Lemons.....		5.9
Muskmelons.....		4.6
Oranges.....		8.5
Pears.....		12.7
Persimmons, edible portion.....		31.5
Raspberries.....		12.6
Strawberries.....		7.0
Watermelons.....		2.7
Fruits, dried:		
Apples.....		65.1
Apricots.....		62.5
Dates.....		70.6
Figs.....		74.2
Raisins.....		68.5
Nuts:		
Almonds.....		9.5
Brazil nuts.....		3.5
Butternuts.....		.5
Chestnuts, fresh.....		35.4
Chestnuts, dried.....		56.4
Cocanuts.....		14.3
Cocanut, prepared.....		31.5
Filberts.....		6.2
Hickory nuts.....		4.3
Pecans, polished.....		6.2
Peanuts.....		18.5
Pinon (pinus edulis).....		10.2
Walnuts, black.....		3.0
Walnuts, English.....		6.8
Miscellaneous:		
Chocolate.....		30.3
Cocoa, powdered.....		37.7
Coffee, infusion (1 part boiled in 20 parts water).....		1.4

Milk.—Milk, on account of its lactose or milk sugar content amounting to 5 per cent., is not an indifferent food for diabetics, and the so-called “milk cures” may prove harmful. If good follows them it is due rather to the incidental underfeeding increasing the tolerance for sugar than to any better utilization of milk sugar over other forms of carbohydrate. Attempts have been made to obtain sugar-free milk. Williamson recommends the following method for preparing a sugar-free milk: Mix 3 or 4 tablespoonfuls of fresh cream with a pint of water in a glass. After from 12 to 24 hours remove the fat that has collected on the surface and mix with an equal volume of water and with white of egg until it has the appearance of ordinary milk. Add saccharin and salt to taste. This mixture contains practically no sugar. Kefir and kunyss contain comparatively little sugar. In ordinary sour milk and buttermilk, however, the sugar is but little reduced.

Cream.—Cream is of great value in the treatment of diabetes. Although it contains from three to four per cent. of sugar, it is permissible since it is seldom used in large quantities, hardly more than six ounces per day. Aside from its use in tea and coffee it is valuable in the preparation of sauces, etc.

Cheese.—Cheese contains large amounts of fat—15-30 per cent. in the better qualities; those made from sour milk (clabber) contain only about 3 per cent. As the protein content of cheese is double that of meat, a portion of good cheese is equal to $1\frac{1}{2}$ to 2 portions of fatty meat. Grated Parmesan cheese is much used in Europe for “binding” instead of flour.

Butter and Other Fats.—The fats are of great value in the dietetic treatment of diabetes. They are the best means for compensating the body for the loss of sugar through the urine. As they are well borne and have a high caloric value, the amount necessary is not large. Ordinarily about 150 grams may readily be taken in a day, yielding, after allowing for loss in the feces, about 1,200 or 1,300 calories. Fat may be given in the form of butter, cream, and oil (olive oil, salad oil, cod-liver oil).¹ Butter may be used and should be used as an addition to all sorts of allowed foods, especially the vegetables. Von Noorden (*loc. cit.*) has prepared a table showing how much butter or oil can be added to various vegetables without impairing their taste or appearance.

To 125 grams raw weight red cabbage or sauerkraut, 25 grams.

To 125 grams raw weight spinach, 40 grams.

To 125 grams raw weight salad, 30 grams oil.

To 125 grams raw weight beans, 25 grams butter.

To 125 grams raw weight string beans, 40 grams butter.

¹ In acidosis the fats are, however, contraindicated; they, furthermore, should be given cautiously after the fasting treatment, as will be pointed out later.

Bacon.—There is marked difference between fat and lean bacon. The fat contains 92 per cent. fat and the lean only 7 per cent. Bacon may be added to vegetables, to meats, poultry, salads, etc.

Meat.—Meat in cooking or roasting loses about 25 per cent. water. Five hundred grams cooked meat are equal to about 650 grams raw. Lamb and pork contain much fat. Venison, being poor in fat, has a lesser caloric value. Poultry, except that especially fattened, is also poor in fat. Fish is for the most part poor in fat, though a few have a high fat percentage—the eel 25 to 30 per cent. Sweetbreads are similar to beef in protein and fat content. Liver, except in small amounts, is excluded by reason of its glycogen. Pâté de foie gras is rich in fat and poor in glycogen, hence allowable. Although meat belongs to the staples of the diabetic's diet, it must not be used in large amounts, especially in severe cases and in those with acidosis, both types requiring a substandard protein allowance, i.e., less than 1 gram per kilo. of body weight.

Eggs.—Eggs weigh from 50 to 60 grams apiece and contain 13 per cent. protein, 10-15 per cent. fat in the whole egg, and 35 per cent. in yolk, and no carbohydrate. Their nutritive value is greater than that of meat by reason of the high fat content. The caloric value of one egg is 75 calories. It might be mentioned that Lüthje claims that the yolk may raise the glycosuria through its content of lecithin, but I believe that this point may be disregarded.

Vegetables.—In the modern treatment of diabetes the vegetables assume a prominent place in the dietary. They subserve three distinct purposes: They satisfy in part the craving of the diabetic for food, they stimulate peristalsis, and they are an excellent vehicle for fat. Those vegetables are to be chosen which contain less than 5 per cent. carbohydrate. Even a part of this may be removed by boiling the vegetables in water and pouring the water off. (See table of vegetables.) The cellulose of vegetables, a carbohydrate, does not seem to augment the glycosuria, although it is probably in part digested in the intestines (Schmidt and Loerisch).

Alcohol.—Much has been written on the use of alcohol in diabetes. It is certain that alcohol as such does not unfavorably influence the elimination of sugar. Its high caloric value, one gram equaling seven calories, makes it a valuable adjunct in the dietetic treatment. It seems to favor the tolerance for fats, and, as von Noorden says, it compensates the diabetic patient for other deprivations.

It makes but little difference in what form the alcohol is taken, provided that the sweet wines and the malt liquors are excluded. Among sweet wines to be forbidden may be mentioned port, Madeira, and Tokay. Whiskey, brandy, Moselle and Rhine wine, and most of the red wines may be permitted. Beer and similar beverages contain carbohydrates that are badly utilized. They are therefore not permitted except in the mildest cases or perhaps during coma. The amount of alcohol estimated as

absolute alcohol that a patient may be allowed is from 30 to 70 grams per day (1 to 2 oz.).

The following table gives the carbohydrate content and caloric value of the more important alcoholic beverages:

TABLE VII
Carbohydrate Content and Caloric Value of Alcoholic Beverages

	Per 100 Grams	
	Carbohydrate	Calories
Beer.....	4.0	41
Moselle and Rhine Wine.....	0	57
French Red Wine.....	1.0	65
Champagne.....	12.0	120
Port Wine.....	5.8	149
Cognac.....	0.7	298
Liqueurs.....	28-34	300-440

Nuts.—Most of the nuts, such as almonds, butternuts, Brazil nuts, filberts, pecans, hickory nuts, walnuts, hazel-nuts, cocoanuts, peanuts, are valuable additions to the food of diabetics. Chestnuts must be excluded because of the large quantity of starch they contain. Jaffa, of the University of California (U. S. Dep. of Agriculture, Farmers' Bulletin 332), has made a very thorough study of the composition and food value of nuts (*see* Table VIII).

TABLE VIII
Edible Portion of Nuts (Jaffa)

	Water	Protein	Fat	Carbohydrates		Ash
				Sugar, Starch, Etc.	Crude Fiber	
	%	%	%	%	%	%
Butternut.....	4.5	27.9	61.2	3.4		3.0
Brazil nut.....	4.7	17.4	65.0	5.7	3.9	3.3
Pecan nut.....	3.4	12.1	70.0	8.5	3.7	1.6
Hickory nut.....	3.7	15.4	67.4	11.4		2.1
Filbert.....	5.4	16.5	64.0	11.7		2.4
Cocoanut.....	13.0	6.6	56.2	13.7	8.9	1.6
Almond.....	4.9	21.4	54.4	13.8	3.0	2.5
Pistachio.....	4.2	22.6	54.5	15.6		3.1
Walnut.....	3.4	18.2	60.7	13.7	2.3	1.7
Walnuts, black.....	0.6	7.2	14.6	3.0		0.5
Walnuts, English.....	1.0	6.9	26.6	6.8		0.6
Chestnuts, fresh.....	43.4	6.4	6.0	41.3	1.5	1.4
Chestnuts, dry.....	6.1	10.7	7.8	70.1	2.9	2.4
Chestnut flour.....	7.8	4.6	3.4	80.8		3.4

The composition of peanuts as found by different analysts is given in the following table:

TABLE IX
Peanuts (Edible Portion)

	Water	Ash	Ether Extract (Fat)	Protein (Nitrogen × 6.25)	Carbo- hydrates	Fiber
	%	%	%	%	%	%
Atwater.....	6.90	1.50	20.10	19.50	18.50	
Atwater and Bryant.....	9.20	2.00	38.60	25.80	24.40	2.50
Jaffa.....	7.40	2.20	43.50	29.80	14.70	2.40
Fetterolf.....	3.05	2.30	49.99	31.00	13.66	

The following table of the composition of shellfish may prove useful:

TABLE X
*Shellfish, Fresh*¹

	Water	Protein (N × 6.25)	Fat	Carbohy- drate
Clams, long, in shell, as purchased, average.....	49.9	5.0	0.6	1.1
Crabs, hardshell, whole, edible portion.....	77.1	16.6	2.0	1.2
Lobster, whole, average.....	79.2	16.4	1.8	0.4
Oysters in shell, average.....	86.9	6.2	1.2	3.7
Terrapin, edible portion.....	18.3	5.2	0.9	

¹ Atwater and Bryant.

Bread.—Many laymen think that toast is allowable, though fresh bread is not. This, of course, is a mistake. The unleavened bread, or matzos, used by the Jews during the Passover holidays, should also be prohibited. In a patient under my observation who had been sugar-free for a long time on a normal diet, the eating of unleavened bread and the drinking of sweet wines customary during these holidays brought about a return of glycosuria.

Many efforts have been made to find a substitute for baker's bread. Notwithstanding, however, the claims of manufacturers that their preparations are starch-free and safe for diabetics, analyses show that both the diabetic breads and the diabetic flours contain starch. It is indeed difficult to make a satisfactory "bread" containing less than 30 per cent. carbohydrate. The much used German "Lufbrot" or air bread contains about 33 per cent. starch. An instructive table regarding the composition of commercial diabetic bread and flour has been published by D. W. Fetterolf (*see* Table XI). An analysis of European, more particularly German, diabetic foods has been made by Magnus-Levy. Contrary to the statement of manufacturers the majority of diabetic breads do not contain more fat than normal bread; yet it is desirable that the fat content of such bread should be increased. Magnus-Levy thinks that two kinds of diabetic bread are sufficient for practical purposes: one with a maximum content of starch of 30 per cent., half the normal; and one real

bread substitute with either five or ten per cent. starch. With a content of less than 5 per cent. a palatable bread food cannot be made. Of the bread containing 30 per cent. starch the diabetic may eat twice as much as of the ordinary bread or rolls with 60 per cent. Such an increase in the bulk of bread is an advantage for many patients. It is desirable that the diabetic foods should present a better guarantee of their composition than is now the case. The analyses should be made only in recognized scientific institutes.

Nicholson finds that a very nice bread can be made of peanut flour and casein, after the following formula: peanut flour, 8 ounces; casein, 2 ounces; a pinch of salt; white of eggs, 12 ounces. The white of egg is beaten to a snow and then the other ingredients (previously lightly mixed) are slowly added.

TABLE XI

Fetterolf (University of Pennsylvania Medical Bulletin, Sept., 1909), United States Products. Analysis of Material as Purchased.

Material	Manufacturer	Protein (Nitrogen × 6.25)	Carbohydrate Including Fiber (by Difference)
Pure gluten flour.....	Battle Creek Sanitarium Food Company, Michigan.....	% 78.75	% 12.62
40 per cent. gluten flour....	Battle Creek Sanitarium Food Company, Michigan.....	39.00	50.16
Self-raising 40 per cent. gluten flour.....	Battle Creek Sanitarium Food Company, Michigan.....	38.69	50.10
20 per cent. gluten flour....	Battle Creek Sanitarium Food Company, Michigan.....	21.00	68.25
Pure gluten biscuit.....	Battle Creek Sanitarium Food Company, Michigan.....	48.31	39.06
40 per cent. gluten biscuit...	Battle Creek Sanitarium Food Company, Michigan.....	36.37	51.94
Potato gluten biscuit.....	Battle Creek Sanitarium Food Company, Michigan.....	75.63	13.23
Pure gluten flour, "Glutosac"	The Health Food Company, N. Y. .	35.25	55.03
Gluten flour.....	Unknown, Danville, N. Y.....	15.50	70.83
Diabetic flour.....	Farwell & Rhines, N. Y.....	11.97	76.41
Diabetic biscuit flour.....	Unknown.....	75.25	5.89
Plasmon meal.....	Plasmon Company of America, New York City.....	78.65	None
Wheat Flours for Comparison:			
Wheat flour, "Hungarian".....			74.70
Wheat flour, patent roller process, high grade.....	Average.....	11.20	74.90

Williamson recommends the following formula: soluble casein, 3 tablespoonfuls; gluten flour, 2 tablespoonfuls; baking powder, $\frac{1}{2}$ teaspoonful; 1 egg well beaten; a small pinch of salt. Mix well together, adding the baking powder last. A little water may be added if necessary. Drop into six tins and bake twenty minutes. Williamson advises that diabetic patients should not try one bread substitute only, but several until the most palatable for the individual patient is obtained.

A fairly palatable bread substitute may be made from almond flour according to the following formula:

Take three cups of almond flour, a pinch of salt, and a pinch of saccharin. Beat up three eggs in a pan, add a cup of milk to the eggs, then the flour, and stir to make a soft batter. Spread the batter about three-quarters of an inch thick, using a pan about nine by twelve inches in size.

Soja.—Soy flour is derived from the fruit or seeds of the *Soja hispida*, a leguminous plant of the order *Phaseolaceae* cultivated in China and Japan. The seeds contain an unusual amount of protein (30 to 35 per cent.) and a small amount of carbohydrate (about 6 per cent.), besides a fatty oil, lecithin, etc. Their nutritive content varies, however, considerably. In Japan the seeds are largely used as a vegetable, but they leave an unpleasant taste. In this country they are used as fertilizer, the seeds being sown and after growth plowed under.

There is at present on the market a proprietary preparation called sarton which is said to be free from starch and sugar and is more palatable than the original seed. It occurs in the form of a powder or paste and may be used in the preparation of soups. Sarton seems to stimulate intestinal peristalsis without causing the formation of gas, a quality of distinct advantage in diabetic patients. Tests with sarton (von Noorden and Lampé) show that in mild cases the elimination of sugar is not influenced by it. In cases of moderate severity, sugar-free on a strict diet, from 80 to 100 grams are well tolerated.

Soja bean flour unfortunately has a disagreeable odor. Useful directions for making gruels, broths, and muffins will be found in an article by Friedenwald and Ruhräh.

The following is an analysis of Soy Bean Gruel Flour, furnished by the manufacturers, the Cereo Co., of Tappan, N. Y.:

Proteids ($N \times 6.25$), 44.64 per cent.

Fat, 19.43 per cent.

Mineral Matter, 4.20 per cent.

Moisture, 5.26 per cent.

Crude Fiber, 2.35 per cent.

Cane Sugar, 9.34 per cent.

Nonnitrogenous Extract, 14.78 per cent.

Starch, none.

Reducing Sugar, none.

Substitutes for Sugar and Vegetable Starch.—Many attempts have been made to replace the ordinary types of vegetable starch—the chief source of sugar in the body—with other forms of starch, in the hope that they would be better utilized by the diabetic. There are certainly differences in the assimilability of the different forms of starch, but they

are not well understood. Below are a few of the substitutes that have been suggested:

LEVULOSE.—While some maintain that this is better tolerated than glucose, others find no difference between the two substances. In every case in which levulose is ordered tests should be made of its tolerance. Von Noorden recommends it in cases of diabetic coma, 100 grams by the mouth, or subcutaneously in a 10 per cent. solution. As most of the fruits contain their sugar in the form of levulose, they may be used when levulose is to be given.

MILK SUGAR.—For a time this was thought to be harmless, but it has been definitely shown that it has the same effect as glucose and starch, hence “milk cures” are harmful for diabetics. In the few cases in which good results have been obtained, they were probably due to the incidental underfeeding affecting the sugar tolerance favorably.

INULIN.—Inulin is a polysaccharid of levulose. It is the chief constituent of certain tubers, e.g., helianthus, topinambur, stachys, black root, artichoke, dandelion, etc. In the opinion of Strauss inulin is more readily assimilated than other vegetable starch. Strauss made a careful study in several cases using at first pure inulin and then inulin-containing plants and found that both had a distinctly favorable influence upon the elimination of sugar and upon acidosis. In the following table is given the composition of the various inulin-containing tubers:

TABLE XII

	Water	Reducing Sugar	Inulin	Nitrog- enous Sub- stances	Pure Proteid	Fat and Fibers	Ash
	%	%					
Helianthus—weak tubers.....	69.77	0	19.85	4.33	2.86	1.77	1.56
strong tubers.....	67.85	0	16.87	3.80	2.75	1.74	2.00
white tubers.....	71.75	1.96	20.12	4.04	1.73		1.46
red tubers.....	82.09	1.41	8.01	3.64	1.90		1.25
Topinambur tuber.....	72.62	0.17	12.91	1.97	0.81		1.89
Dahlia tuber.....	83.34	1.27	10.32	0.74			1.38

Regarding the preparation of the helianthus tubers Strauss found that patients preferred them roasted like potatoes, though they were also readily taken when boiled in salt water and served with hollandaise sauce or with mayonnaise dressing. They may be given as purée, or as salad with oil and vinegar. The price of inulin and of the inulin-containing vegetables is high, but if the cultivation of the plants is encouraged the price ought soon to become more reasonable. Strauss believes that inulin will be found especially valuable when acidosis is present.

Substitutes for Sugar.—As a substitute for sugar saccharin, an anhy-

drid of orthosulphamidbenzoic acid (benzoyl sulphonieimid) is in general use. It occurs as a white crystalline powder, nearly odorless, having a sweet taste even in very dilute solutions. It is soluble in 250 parts of water and in 25 parts of alcohol, and is said to be 300 times sweeter than sugar. It is not converted into glucose in the body. In a careful study of the influence of saccharin on digestion, metabolism, nutrition, and general health, made by the Referee Board of Consulting Scientific Experts of the Department of Agriculture, the following conclusions were reached:

(1) Saccharin in small quantities (0.3 gram per day or less) added to the food is without deleterious or poisonous action and is not injurious to the health of normal adults, so far as is ascertainable by available methods of study.

(2) Saccharin in large quantities (over 0.3 gram per day and especially above 1 gram daily) if taken for considerable periods of time, especially after months, is liable to induce disturbances of digestion.

(3) The admixture of saccharin to food in small or large quantities has not been found to alter the quality or strength of the food. It is obvious, however, that the addition of saccharin to food as a substitute for cane sugar or some other form of sugar must be regarded as a substitution involving a reduction of the food value of the sweetened product and hence as a reduction in its quality. For many people saccharin has an after taste more or less bitter that makes it objectionable.

Other substitutes for sugar are crystallose and dulcin. The latter is about as sweet as saccharin but has slightly toxic properties.

Hediosit, glucoheptonic acid, is a seven carbon-atom sugar readily oxidized in the diabetic organism. It has been recommended by Rosenfeld not only as a sweetener of foods, but also as an antiketogenic agent. It warrants further study.

CLASSIFICATION OF DIABETES

Various classifications of diabetes have been proposed. In practice, I have found the following satisfactory:

1. Mild diabetes—this is a type in which the sugar is easily removed from the urine, and does not return when a considerable amount of carbohydrate is given in the diet. The tolerance for carbohydrate in other words is high. This type is most common in adults of middle life, but occurs in adolescents and occasionally in children. It matters little how high the initial percentage of sugar is when the patient first comes under observation.

2. Moderately severe diabetes—that in which there is a very small carbohydrate tolerance, the patient being sugar-free on a diet of protein and fat and a very small amount of carbohydrate.

3. Severe diabetes—one in which the sugar-tolerance is nil, and in which on a carbohydrate-free diet, the urine contains sugar derived from protein.

4. Grave cases—those in which there are marked evidences of acidosis—the ferric-chlorid reaction in the urine and symptoms of acid intoxication.

TREATMENT

GENERAL PRINCIPLES

The ideal of treatment of any disease is the removal of the cause. In diabetes this is not possible for the cause is unknown. We must therefore be content to work for the removal of the principal symptom—the glycosuria, the lessening or abolishing of which means the lessening or abolishing of the hyperglycemia, the main factor responsible for the symptoms of the disease. This object—the removal of the sugar from the urine—can be accomplished only by a proper dietetic regimen. Drugs alone are powerless to do it. The diet must be so adjusted to the impaired metabolism as to render the urine sugar-free without injuring the general health of the patient.

Diabetes cannot be treated in a schematic or routine manner. The cases differ and must be treated individually. The patient must be informed of the importance of diet in the treatment, and it must be made plain to him that his salvation is altogether in his own hands; that occasional sugar or bread orgies hurt him and no one else; that he cannot undo the harm of a lapse from dietetic virtue by subsequent strict asceticism; that such indulgences may overtax his tolerance permanently and put it a peg lower. In no disease is the patient to be warned more against quackery and quack remedies, for the harm of improper treatment cannot be well retrieved. He should be told once for all that there is no drug that will cure diabetes and that most of the bread substitutes and other diabetic foods contain an amount of starch that is not negligible.

Many physicians are inclined to be lax, and as long as the amount of sugar eliminated is small, they permit the patient to be liberal in his diet. By some this is done from a desire to keep the patient ignorant of the real nature of his malady; by others from a lack of interest or firmness or knowledge of the disease. This attitude, whatever the motive, is unjust to the patient. Bad results may not follow at once, but they are sure to come. Diabetes is a disease against which the plan of battle must be laid not for a month or a year, but for a decade, indeed for a lifetime. To tell a patient that he must live on such and such a diet and then let him shift for himself is not fulfilling one's duty. The fact must be brought home to him that if he wants to keep the disease under control he must

be vigilant for all his days. It is of course essential before the patient is told he has diabetes that his case be studied so thoroughly that the conclusion is unequivocal. The various dire complications that may occur in the course of diabetes need not be foretold—nothing is to be gained by alarming the patient, unless he will not obey instructions, in which event it is usually justifiable to scare him into good behavior. It is in this way that some of the diabetic foods and vaunted remedies achieve good results: A patient who persists in disregarding the physician's gentle advice will often carry out conscientiously the very strict dietetic instructions printed in the minatory literature accompanying proprietary articles. For the improvement that follows he will give credit to the remedy and not where it belongs—to care in diet.

Diabetes is easily discovered if the patient presents one or more of the suggestive symptoms—thirst, itching, boils, carbuncles, gangrene—but as many do not have any characteristic complaints, it follows that diabetes may be overlooked unless the physician makes it a habit to examine the urine of every patient, regardless of age, for sugar. Some of the less common symptoms that may constitute the inaugural symptoms of the disease, to use a phrase of Moynihan's, are impotence, neuritis, neuralgia, sciatica (especially double sciatica), falling out of the teeth, rapid emaciation, and stupor and coma. I have seen four cases in which the first and only symptom was impotence. If on the first examination sugar is found the patient should be instructed to collect the urine for twenty-four hours, to measure it, and to send a sample of the whole amount.

The amount of sugar found in the urine when a patient first presents himself is no criterion of the gravity of the disease. A man, H. W., 56 years of age, came to me with ten per cent. sugar without diacetic acid or acetone. He complained of nothing in particular but only came because he had been told that he had diabetes. Within one week, under a carbohydrate free diet—it was just before the Allen treatment came into vogue—the sugar disappeared. Recently a woman, Mrs. M. L., 54 years old, of Lancaster, Pa., consulted me on account of rheumatic pains of the shoulders and fingers. Her urine, much to her surprise and mine, contained 10 per cent. of sugar. On the Allen treatment she lost her sugar completely within seventy-two hours.

If sugar is discovered in the urine the case may be conducted in the following way: It should first be determined whether sugar is constantly present or whether the case is one of transient glycosuria. This can readily be done by examining a night and a morning specimen or, preferably, a specimen of the twenty-four-hour collection, for several successive days, while the patient is on his ordinary diet. If sugar is found repeatedly, even though it is not present in every specimen, the case may be looked upon as one of diabetes. Should the first examination

have shown in addition to large amounts of sugar the presence of diacetic acid, it may be wiser, instead of taking several days for studying the case, to place the patient at once upon treatment for acidosis, which is described on another page.

Physicians should be familiar with the possible complications of diabetes so that at the earliest moment steps may be taken to combat them.

It goes without saying that a study of the case that limits itself to an examination of the urine is entirely inadequate. A thorough general examination of the body must be made, which will include the blood, the blood pressure, the eyes and eye grounds, the nervous system, and the lungs. A Wassermann test is advisable in nearly all cases. The general habits of life of the patient must be investigated: his work, his means and methods of relaxation, his sleep, his sexual life, etc., for the diabetic state is profoundly under the influence of the "psyche." Some writers, indeed, speak of a neurogenic diabetes, but a permanent diabetes on such a basis is rare, if it occurs at all. Temporary glycosurias after cerebral injuries are met with, as already mentioned, but if they pass into confirmed diabetes it is altogether probable that the pancreas or some other diabetogenic organ has become involved. There is, however, no doubt as to the ability of the nervous system to influence sugar production both in health and in diabetes. The pathway from the brain to the splanchnics and the adrenals has been sketched on a previous page. Diabetic patients made sugar-free or in whom the sugar has been greatly reduced often show a return of sugar or an increase after severe nervous shock. Nervous excitement is also capable of precipitating diabetic coma. It is, therefore, of the utmost importance to lessen the strain and fret so common in the life of the American business man. One of my patients, whose business brought him many vexations, improved in a remarkable manner when he took off several days during the week in the summer to go fishing.

Success in treatment lies not alone in instituting the proper dietetic measures, but also in paying strict attention to all bodily functions. The bowels need careful watching, for diabetics are usually constipated. Effervescent citrate of magnesia and other sweetened laxatives are of course out of question. The salines are useful, especially the natural bitter waters, likewise phenolphthalein, which may be combined with rhubarb in capsule form, of each gm. 0.12 to 0.18 (2 to 3 grains). Care should be given to the mouth on account of the danger of pyorrhea alveolaris. Milk of magnesia as a mouth wash and iodine applications, together with skillful sealing of the teeth by a dentist, are beneficial measures. Even trifling wounds should not be neglected, as the lessening of the opsonic index, shown by DaCosta and Beardsley, and by Sisto to occur in diabetes, predisposes to infection.

Under all forms of treatment, or under none, the diabetic patient

should lead as tranquil a life as circumstances permit. He should have plenty of sleep and frequent vacations. I have found more than once that a man who would excrete sugar after eating a slice of bread would be sugar free during a camping trip, even if he ate bread and corn.

The essential point in the dietetic treatment consists in bearing constantly in mind the impaired tolerance of the diabetic for carbohydrates. By not overtaxing this tolerance the power of assimilation for carbohydrates is not only conserved, but in the majority of cases is increased.

The aglycosuric state has an effect on the carbohydrate tolerance, tending to raise it. At the same time the information that his urine has become sugar-free cheers the patient. Yet this knowledge is not without danger, for sometimes patients believe themselves cured and relax in their dietetic abstemiousness.

In making out diet lists for a diabetic patient the physician should remember that the man who finds that he is deprived of bread, potatoes, and similar staples considers himself very much abused and is likely to harp continually on his privations. It is therefore wise to make the allowed list as extensive as possible, so that the patient may be conscious of a wide latitude of choice.

By varying the mode of preparation of the different articles the bill of fare in the individual cases can be still further amplified.

The following is a specimen diet list such as I find useful in many cases :

- ALLOWED:** Plain soups of chicken, mutton, oysters or clams, made without flour, cereals or potato.
Fresh fish, beef, ham, mutton, lamb, oysters, clams, sardines, bacon, all prepared without flour dressing.
Eggs, butter, vegetables such as spinach, string beans, watercress, celery, asparagus, onions, mushrooms, cauliflower, cucumbers, endive, Swiss chard, and sauerkraut.
Desserts: Junket or gelatin, sweetened with saccharin.
Cheese, olives.
Beverages: Tea or coffee without sugar; if desired, with saccharin.
- FORBIDDEN:** Sugar, ice cream, pastry, candy, crackers, macaroni, tapioca, potatoes, parsnips, beets, turnips, preserves and jellies, bananas, plums, sweet wines, cordials, malt liquors, bread, and chestnuts.

One often finds that a patient in whom sugar has returned insists that he has not violated his instructions. In such cases, I have the patient keep an accurate record of all food ingested and bring it to me. Not rarely have I then found that he had taken something that he should not have taken, or more of a permitted article than was allowed. Patients often think, for instance, that toast is permitted when bread is forbidden, because they believe toast to be more digestible.

THE FASTING TREATMENT

Allen, as stated previously, believes diabetes is dependent on a weakness of the pancreatic function which can be strengthened by giving it rest. This rest is secured by starvation. In a suitable case, the patient receives no food whatsoever. He may have water *ad libitum*, and whiskey—although this is not essential—up to from 50 to 250 c.c. in the twenty-four hours. A little black coffee or tea is also permitted. The patient should be at rest, but need not necessarily be in bed, unless he is weak when the treatment is started. The urine collected for twenty-four hours is examined for sugar and for the ferric-chlorid reaction. All emotional strain should be kept away from the patient, and he should be encouraged to bear his fast with equanimity. In many cases the sugar, after three or four meals have been omitted, disappears, even when the initial percentage was large. In other cases, it may require a fast of two days, or even of three, four or five days. Allen has fasted some of his patients as much as ten days. On the third day of a fast, it is well to add a little chicken-broth or meat-broth—300 c.c., divided into two portions. If the urine shows the ferric-chlorid reaction, it may be advisable to give alkalies—sodium bicarbonate, etc.—in doses of one or two grams three times a day, in a little plain water or in Vichy.

Generally acidosis, contrary to what takes place in health, diminishes under the fasting, so that alkalies are not required, or if so, for but a short time. Joslin has lately come to the conclusion that alkalies are quite unnecessary. The disappearance of the ketonuria during starvation may seem paradoxical; but it must be remembered that ketonuria is probably produced by the fats in the diabetic diet, rather than by a deficiency in carbohydrate.

During fasting, most of the annoying symptoms—headache, lassitude, general discomfort, thirst and itching—disappear. Hunger is complained of less than one would expect, in view of the customary craving of diabetics for food.

As soon as the twenty-four hours' urine has become sugar-free, the patient receives an allowance of 150 grams of green vegetables of the so-called five per cent. group (Table XIII). This quantity, in the case of spinach, amounts to about four tablespoonfuls; and in the case of string beans, to five tablespoonfuls. The whiskey may be reduced, and the coffee and broth continued. If no sugar appears, the quantity of the five per cent. vegetables is increased by 150 grams of the five per cent. variety or 90 grams of the ten per cent. variety. Vegetables lose carbohydrate in cooking; so that the five per cent. variety, when cooked, will represent three, and the ten per cent., six per cent. of carbohydrate. By cooking the vegetables in a steamer, the soluble carbohydrate is retained.

If the urine remains sugar free on the vegetable diet, protein may be added on the third day, either in the form of eggs—three in the twenty-four hours, representing twenty grams of protein—or in the form of meat or chicken, increasing gradually until the allowance is about one gram of protein per kilogram of body weight. It is not necessary for the diabetic whose carbohydrate tolerance is low to go up to the normal protein allowance.

Contrary to the former practice, fats are not forced in the Allen method of treatment. He found—and this observation has been confirmed by Joslin, and Stengel, Jonas and Austin—that the early use of fat leads to a return of glycosuria. Fat is, of course, contained in egg and, to a slight extent, it is also contained in meat; but native fat, such as bacon, olive oil, cheese, butter or cream, is best not given until a fair protein intake has been reached. One may begin with two short slices of bacon (30 grams), and increase the fat by this amount until the patient's desire for fat is satisfied without sugar appearing.

If the patient bears the carbohydrate in the five and ten per cent. group of vegetables well, he may have proportionate amounts of those of the fifteen and twenty per cent. group; likewise, of the fruits; and finally, of potato, cereals and bread, always in definite amounts.

Whenever sugar reappears, it is a sign that the tolerance for carbohydrate has been overstepped, and that a fast day is required.

For a successful fasting treatment the coöperation of the patient is essential. Its principles should, therefore, be explained to him. It is a further advantage, if he is taught to test his urine for sugar with Benedict's reagent.

While under treatment, the patient must be carefully watched for any untoward symptoms. Vomiting, restlessness and drowsiness are danger signals. If they develop, it is best to interrupt the fasting and give the patient some form of carbohydrate—preferably, a single form, such as oatmeal or milk. Sometimes a patient shows no improvement, and may even show retrogression, under the treatment. If the fasting is then interrupted, and the patient placed either on a carbohydrate or on a mixed protein-fat diet for a few days, he may respond to a second fast with a striking improvement. One of the best illustrations of such a result is the case of Geyelin and DuBois.

If the patient remains sugar-free, he should still have a fast day once a week. This is especially important for patients who cannot, for one reason or another, consult their physician regularly. Not only should they institute this weekly fast day, but they should also fast whenever they discover sugar in the urine.

Many patients, under the Allen treatment, are distressed by loss of weight—mentally distressed, I mean, for physically, the loss in weight does not seem to injure them. Allen believes that a gain in weight is not

of great importance, and that the patient should avoid all attempts to regain his former weight. It is undeniable, however, that a gain in weight, the urine remaining sugar-free, is an excellent psychic tonic for the patient.

Whenever possible, the patient on the Allen treatment should be in a hospital having on its nursing staff a dietician trained in caloric feeding.

In instituting the Allen treatment in a patient's own home it is well to write out specific directions for the patient's or the nurse's guidance. A brief outline of such directions is given below.

Directions for Fasting Treatment.—Take no food for (insert here the number of days of fasting) days. Drink water as much as is desired, and from a teaspoonful to a tablespoonful of whiskey every two hours. A little black coffee or tea may also be taken.

Test the urine with Benedict's reagent for sugar or have it tested, and if sugar-free, break the fast by adding on the first day four tablespoonfuls of spinach, a plate of lettuce, and four or five tablespoonfuls of string beans, and two cups of chicken broth or beef broth. The whiskey may be continued, perhaps in reduced amounts. Test the urine daily and if no sugar appears add to the diet two or three eggs and more vegetables from the five and ten per cent. groups. (A list of these should be given to the patient.)

The physician should be in constant touch with a patient who is on the Allen treatment and the urine should be examined daily for sugar as well as for diacetic acid.

The Allen treatment is most useful:

(a) In recent cases of diabetes regardless of the percentage of sugar.

(b) In cases that cannot be made sugar-free by the ordinary dietetic treatment. Under the older methods, a fair proportion of cases had small amounts of sugar in the urine that refused to be driven out. With the Allen treatment, taken under proper precautions and continued for a sufficient length of time, the number of cases that do not become aglycosuric is very small. The stubborn ones are those in which the patient has been treated fairly well, but not perfectly, before the Allen method is begun.

At the present time, in this country at least, the Allen method is the one most frequently employed. Not only is it usually safe, but, as Christian points out, it saves the patient and the hospital from one to two weeks of time.

TABLE XIII

Foods Arranged Approximately According to Per Cent. of Carbohydrates

VEGETABLES ¹

5 per cent.		10 per cent.	15 per cent.	20 per cent.
Lettuce	Vegetable	Onions	Green peas	Potatoes
Spinach	marrow	Turnip	Artichokes	Shell beans
Sauerkraut	Cauliflower	Carrots	Parsnips	Baked beans
String beans	Tomatoes	Okra	Lima beans	Green corn
Celery	Rhubarb	Mushrooms		Boiled rice
Asparagus	Egg plant	Beets		Boiled maca- roni
Cucumbers	Leeks			
Brussels	Beet greens			
sprouts	Watercress			
Sorrel	Cabbage			
Endive	Radishes			
Dandelions	Pumpkin			
Swiss chard	Kohl-rabi			
Sea kale	Broccoli			

FRUITS

Ripe olives (20 per cent. fat)	Lemons	Apples	Plums
Grapefruit	Oranges	Pears	Bananas
	Cranberries	Apricots	
	Strawberries	Blueberries	
	Blackberries	Cherries	
	Gooseberries	Currants	
	Peaches	Raspberries	
	Pineapple	Huckleberries	
	Watermelon		

NUTS

Butternuts	Brazil nuts	Almonds	Peanuts
Pignolias	Black walnuts	English	
	Hickory nuts	walnuts	40 per cent.
	Pecans	Beech nuts	Chestnuts
	Filberts	Pistachios	
		Pine nuts	

MISCELLANEOUS

Unsweetened and unspiced
 Pickles
 Clams
 Oysters
 Scallops
 Liver
 Fish roe

Reckon *actually available* carbohydrates in vegetables of five per cent. group as three per cent.; of ten per cent. group as six per cent.

¹ From Joslin, Am. Jour. Med. Sc., October, 1915.

Limitations of the Allen Treatment.—It would be a mistake to conclude that the Allen treatment is infallible. It is neither infallible nor harmless, although in most cases it may be so considered. It appears to be of doubtful utility in the case of elderly, obese persons who have borne their diabetes for ten or twenty years without discomfort, and who, under a restricted diet, excrete only traces of sugar in the urine. A sudden upset in their metabolism is risky and unwise. Such long-standing cases are best treated by diet restriction, and not by prolonged fasting.

Very obese patients sometimes develop a dangerous degree of acidosis on fasting, their ketones being derived from the breakdown of their body fat.

NON-FASTING TREATMENT

Where fasting is not employed and the patient is treated by the older method of carbohydrate restriction, he should receive a dietary of fat and protein based on Table V. A specimen menu for the three meals of the day is given in Table XIV (Standard Strict Diet). Or one may give the patient, if his condition is not serious, a general diet-list, from which he shall select his own meals for two or three days. He must keep a strict record of what he eats. When he returns, he must bring with him this record, together with a record of the daily urinary output and a sample of his urine. If he is found to be sugar free, it is advisable to continue the same diet for a few days longer, and then to begin the addition of definite amounts of carbohydrate. Most patients appreciate being allowed to have a slice of bread, which weighs about 30 grams, and contains sixty per cent., or 18 grams, of carbohydrate.

Oatmeal Treatment.—The oatmeal treatment, introduced into the dietotherapy of diabetes by von Noorden, accomplishes good results in certain types and stages of the disease. Very little is known as to its real mode of action. The results are better than those that have been obtained with the rice diet of Duering, the potato diet of Mossé, or the milk cure of Donkin. The sugar assimilation seems to be better when only a single type of carbohydrate is offered to the system than when a variety of starches is ingested at the same time. Magnus-Levy has shown that the active substance in the oatmeal is the oat starch, and believes that the good results are due to fermentation of this starch in the intestines, the absorbed fermentative products either being oxidized in place of sugar or acting as stimulants to sugar combustion. Von Noorden thinks that oatmeal has a specific effect on the carbohydrate metabolism in the liver. Naunyn denies that the diabetic possesses an elective tolerance for oatmeal, holding that the good effects are due to fermentative products formed from the oatmeal in the intestines. Blum found that equally good results could be obtained with wheat flour as with oatmeal, provided the treatment was preceded by several vegetable days and that no meat was given

with the wheat flour. He found wheat and oatmeal better assimilated if the general condition of the patient was good. In his opinion the better assimilation is due to the diminution of the hyperglycemia brought about by the preliminary vegetable days. The lessening of the hyperglycemia increases sugar combustion.

TABLE XIV
*Standard Strict Diet*¹

Meals, Articles, Amounts (Rough Measure)	Protein	Fat	Carbo- hydrate	Calories	Total
	Grams	Grams	Grams		
Breakfast					
Coffee					
Cream, 40 gm., or 2 tablespoonfuls.	1.48	10.28	1.42	108	
Eggs, 2, 100 gm.	13.40	10.50		152	
Butter, 15 gm., or 1 ball.	0.15	12.75		119	
Ham, fried, 100 gm., 1 slice.	23.31	34.86		400	
Luncheon					779
Bouillon, 120 gm., 1 cup.	2.64	0.12	0.24	13	
Egg, 50 gm.	6.70	5.25		76	
Tenderloin steak, 100 gm., 1 slice.	23.50	20.40		286	
Bacon, 30 gm., 1 slice.	3.15	19.44		194	
Spinach, 100 gm., 2 tablespoonfuls.	2.10	4.10	2.60	57	
Butter, 15 gm., 1 ball.	0.15	12.75		119	
Dessert made from egg, 50 gm.	6.70	5.25		76	
Cream, 40 gm., 2 tablespoonfuls.	1.48	10.28	1.42	108	
Afternoon tea					929
Tea					
Cream, 20 gm., 1 tablespoonful.	0.74	5.14	0.71	54	
Dinner					54
Consommé, 120 gm., 1 cupful.	3.00		0.48	14	
Mackerel, fresh, 100 gm., a portion.	21.80	5.90		144	
Butter, 15 gm., 1 ball.	0.15	12.75		119	
Mutton, (roast leg), 75 gm., 1 slice.	18.75	16.95		234	
Asparagus, 125 gm.	1.88	0.13	3.50	23	
Butter, 15 gm., 1 ball.	0.15	12.75		119	
Lettuce, 50 gm.	0.60	0.15	1.45	10	
Olive oil, 13 gm., 1 tablespoonful.		13.00		121	
Cheese, 20 gm., 2 scoops.	5.98	7.78		99	
Demi-tasse of coffee.					883
	137	220	12		2645

¹ Modified from Jansway (Am. Jour. Med. Sci., Mar., 1909). Caloric values after Locke (Food Values, New York, 1911).

$$\begin{array}{lcl}
 \text{Protein} \dots\dots\dots 137 \times 4.1 = & 561 & \text{Calories} \\
 \text{Fat} \dots\dots\dots 220 \times 9.3 = & 2046 & \text{"} \\
 \text{Carbohydrate} \dots\dots 12 \times 4.1 = & 49 & \text{"} \\
 & \hline
 & 2656 & \text{"}
 \end{array}$$

The addition of meat to the oatmeal diet lessens its usefulness, since meat, according to Blum, has an unfavorable influence upon the oxidation of carbohydrates. Vegetable albumin inhibits sugar combustion in a somewhat lesser degree than meat (Blum).

The efficacy of the oatmeal treatment is not explained by studies in metabolism. Allen and DuBois found no especial influence of oatmeal in diabetes, and no especial readiness of oxidation in this form of carbohydrate. The respiratory exchange failed to account for all the carbohydrate that disappeared. The behavior of the respiratory quotient showed no important difference on the first day and on the third day of the oatmeal treatment.

The oatmeal treatment is applicable to all cases of acidosis and to severe cases of diabetes in which the exclusion of carbohydrates and protein restriction fail to render the urine sugar-free.

A few days of oatmeal treatment may in severe cases help to render the urine aglycosuric. At times no results are seen under the first oatmeal treatment of three or four days, and a second and a third may then have to be instituted (Lampé). In the majority of cases a coexisting ketonuria is diminished. The following table, Table XV, shows the caloric value of the oatmeal diet. In addition to oatmeal and butter, black coffee, tea, lemon juice, and a little red wine may be allowed. The best results with oatmeal seem to be achieved when the treatment is preceded by one or two vegetable or green days.

TABLE XV
Oatmeal Diet

	Protein	Fat	Carbo- hydrate	Calories	Total
	Grams	Grams	Grams		
Butter, 150 grams (5 ounces).....	1.5	127.5		1,190	
Oatmeal (rolled oats), 300 gms. (10-11 oz.)	50.1	21.9	198.6	1,224	
	51	149	199		
Calories.....	213	1,385	816		2,414

The oatmeal is put into 3 pints of water, slightly salted, and thoroughly cooked for at least 6 hours, and, while still hot, strained. The butter is then added and stirred in. It is usually taken in 7-ounce feedings at two-hour intervals.

It is rarely possible to continue the monotonous oatmeal diet for more than three or four days at a time; some patients will not take it that long. Another objection to it is that it sets up fermentation with flatulence, and either constipation or diarrhea. The reluctance of the patient may often be overcome by informing him of the good effects likely to follow persistence in the treatment.

As a substitute for oatmeal Klemperer has recently used glucose, giving it under the same conditions and with the same restrictions as oatmeal. From 100 to 150 grams were administered in an equal amount of water. It was found that when meat was withheld, and after preliminary vegetable days, the glucose was assimilated in considerable quantities; but from the statistical data given one is impressed with the fact

that the method is not superior, perhaps not even equal, to the oatmeal diet. It is possible that levulose, used under the same conditions, may prove superior to glucose.

Green Day.—The advantage of the vegetable, or green, day, which in its caloric value is almost equivalent to a fast day, is that it gives rest to nearly all metabolic functions. It thereby raises the tolerance for sugar and lessens the hyperglycemia. It may take the place of the fast day when the Allen treatment is not employed. The daily ration for a green day is three eggs, thirty grams of bacon, 15 c.c. of olive oil, a cup of clear broth, and coffee or tea, with green vegetables of the five per cent. group. A specimen green day is given in Table XVI.

TABLE XVI
Green Day

	Protein	Fat	Carbo- hydrate	Calories	Totals
Breakfast	Grams	Grams	Grams		
1 egg, boiled or poached, 50 grams.....	6.70	5.25		76	
Cup of black coffee					76
Dinner					
Spinach, 100 grams, 2 tablespoonfuls...	2.10	4.10	2.60	57	
1 egg, 50 grams.....	6.70	5.25		76	
Bacon, 15 grams, ½ slice.....	1.57	9.72		97	
Lettuce, 50 grams.....	0.60	0.15	1.45	10	
Olive oil, 13 grams, 1 tablespoonful....		13.00		121	
Afternoon					361
Bouillon, 120 grams, 1 cup.....	2.64	0.12	0.24	13	
Supper					13
1 egg, scrambled.....	6.70	5.25		76	
Butter, 7½ grams; ½ ball.....	0.07	6.37		59	
Bacon, 15 grams, ½ slice.....	1.57	9.72		97	
Asparagus, 125 grams.....	1.88	0.13	3.50	23	
Cup of tea					255
	31.00	60.00	8.00		705
Calories	125	549	28		

The Potato Treatment.—Mossé, in 1902, recommended a potato diet for diabetes, but the treatment did not become popular and was replaced by the oatmeal cure of von Noorden. Like the latter, it offers a single carbohydrate. It has the advantage of being a bulky food, and as its use involves a certain amount of undernutrition, it is an approach to fasting.

Patients often appreciate a potato more than they do bread; and as the potato contains only one-third as much carbohydrate and may be given in a variety of ways, with butter, lard, etc., it is an excellent food for cases in which there is a considerable carbohydrate tolerance.

Bananas.—The banana, which contains twenty per cent. of carbohydrate, has been advocated as a substitute for oatmeal by von Noorden. Whenever employed, the banana should not be soft or over ripe, as in that state the starch has been converted into sugar. One banana contains about twenty grams of carbohydrate.

TABLE XVII
Constituents of a Strict Carbohydrate-Free Diet

ALLOWED	
Eggs	Butter
Meat, including bacon and ham	Cheese ¹
Fish	Olive oil
Broth	Tea
Gelatin	Coffee

To this may be added cream, containing about three per cent. carbohydrate, and the vegetables of the five per cent. group, which, by boiling, can be reduced to a carbohydrate content of three per cent.

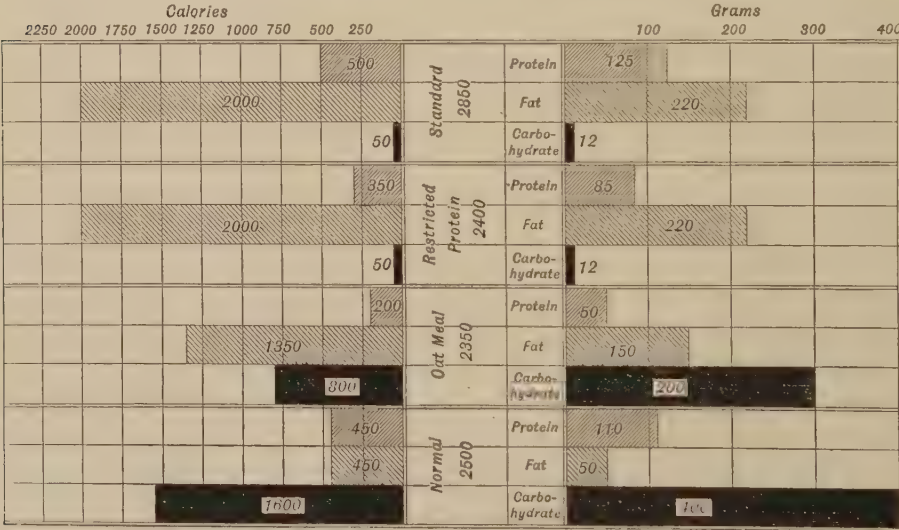


FIG. 2.—ILLUSTRATING THE QUANTITATIVE RELATIONS AND THE CALORIC VALUES OF THE NORMAL AND OF VARIOUS DIABETIC DIETS.

TREATMENT OF ACIDOSIS AND COMA

Coma is the most serious complication that can occur in the course of diabetes. The prognosis is almost uniformly bad. I have, however,

¹ Cottage cheese, cream cheese and skim-milk cheese contain from 2.2 to 4.3 per cent. carbohydrate. American red cheese, Dutch cheese and Limburger cheese are practically carbohydrate free.

seen recovery in two instances. As the preventive treatment gives immeasurably better results than measures used after the condition is established, every effort should be made to learn when coma is impending. Frequently the coma is preceded by premonitory symptoms; restlessness; abdominal pain, sometimes simulating appendicitis; shortness of breath; irritability, staggering, dizziness, sudden intense thirst, yawning, pain in the limbs, headache, and drowsiness. In every case of coma of unknown cause a diabetic origin should be suspected and the proper urinary tests made. It should, however, be remembered that not every attack of coma in a diabetic is necessarily due to acidosis. It may be due to uremia, to apoplexy, or to obstruction of an arteriosclerotic vessel in the brain. A fruity, aromatic, or chloroformlike odor on the breath is suggestive, even more so is a peculiarly deep breathing (Kussmaul's breathing), but the most valuable sign is the discovery of sugar and diacetic acid in the urine. A soft eyeball, though not invariably present, is also a valuable sign of diabetic coma (Riesman).

Albuminuria and cylindruria are almost constant in diabetic coma, and indicate a toxic irritation of the kidney.

Any accident or complicating disease arising in the course of diabetes always involves the danger of coma. Therefore, the patient should be instructed to call a physician even in the case of the most trivial ailment or accident, so that the necessary precautions may be taken,—a fact to bear in mind in expressing a prognosis. I once saw an attack of influenza throw a woman who had been diabetic for over twenty years into fatal coma.

The urine of every diabetic patient should be regularly examined for the ferrie-chlorid reaction. If, in addition to a positive reaction, there are the signs of acidosis previously described, prompt and energetic treatment should be instituted.

The patient should be put to bed and should be guarded against every form of excitement. The bowels should be moved with an enema or a saline—Epsom salts or one of the more active mineral waters. Joslin recommends that the liquids ingested be warmed, that the calories necessary to raise cold liquids to body temperature may be saved. The administration of alkalies should be begun at the earliest possible moment, as they accomplish infinitely more in the prodromal stages of coma than afterwards. It is preferable to give sodium bicarbonate in doses of a teaspoonful every hour by the mouth, or about fifty grams by rectum at least twice in the first twenty-four hours. About one hundred grams should be given each day for two or three days. For oral administration it may be given in a little Vichy. If the rectal route is used, the solution, usually in the strength of about forty or fifty grams to the liter of sterile tap-water or normal salt solution, may be given either *en masse* or by the Murphy drip method. In the latter case the solution must be kept warm constantly.

The alkali may also be given intravenously, from 1,000 to 1,500 c.c. of a four per cent. solution in a previously sterilized normal salt solution being thrown into a vein. It is said that convulsions and collapse sometimes follow the intravenous use of sodium bicarbonate, but this is such a rare occurrence that it should not deter one from using that method. Sodium bicarbonate solution should not be administered subcutaneously—that is, as hypodermoclysis, since it causes great pain, and sometimes sloughing.

Under intensive alkali treatment, edema, involving the face, trunk and limbs, sometimes develops. The patient looks as if he had acute Bright's disease. When the alkali is stopped the edema disappears.

Instead of the bicarbonate the citrate of sodium, as recommended by Lichtwitz, may be employed for oral administration.

As the patient improves the alkali should be gradually diminished. It is unwise to cut it off too rapidly. Furthermore, a patient who has once had distinct acidosis with symptoms should be kept under observation, and should resort to the use of alkalies whenever, notwithstanding a proper diet, ketonuria returns. Loenig reports the case of a boy of eleven years who, under a strict diet and the use of sodium bicarbonate, had become sugar-free. He continued to take the bicarbonate of soda for some time, and then, contrary to instructions, discontinued it. Two or three days later he became comatose and, despite the energetic introduction of alkalies, succumbed.

Sometimes the urine output diminishes markedly with the onset of coma, the sugar and ketones also showing a decrease. Albumin and casts are very common, and indicate a high degree of toxemia. Diminution in the quantity of urine may, however, be only apparent; for retention is not infrequent. Hence, the bladder region should always be percussed in cases of coma.

The Circulation.—If the pressure is high, nitroglycerin, 0.0006 to 0.0012 (1/100 to 1/50 gr.), is useful. Digitalis, in the form of the tincture, or digipuratum, and caffein sodium benzoate (0.12 to 0.20—2 to 3 gr.) are of value when the circulation fails. They may be given hypodermically. Black coffee, by mouth or by rectum, is also a good stimulant. Oxygen, in my experience, has not relieved the air hunger; but it is a remedial measure that one is often forced to employ.

Bleeding.—Bleeding, especially in high-pressure cases, is an excellent eliminant of comatogenic toxins. From 300 to 500 c.c., or even more, should be taken from a vein at the arm; and while the vein is exposed the intravenous injection of sodium bicarbonate may be given into the upper end of the divided vessel.

Alcohol.—Alcohol is probably antiketogenic and should be used in the treatment of impending coma. The amount administered must be governed by the tolerance of the patient's stomach. As a rule, four to

eight grams (1-2 teaspoonfuls) of whiskey every two hours will be sufficient.

The Diet.—Since it has now been pretty well established that the fats are the source of the ketone bodies, the first thing to do in treating acidosis and combating threatened coma is to withdraw the fats from the diet. The protein intake should be cut down. As regards the carbohydrate, the problem is difficult. If the patient develops acidosis and symptoms of impending coma while on a strict carbohydrate-free diet, and does not improve promptly after the withdrawal of fats and the cutting down of protein, it is advisable to give him a moderate amount of carbohydrate. Experience has shown that when a single form of carbohydrate is given the results are better than when various kinds of carbohydrate food are allowed. It is in these circumstances that the oatmeal treatment of von Noorden or the use of milk is often attended with satisfactory results. Sometimes the fasting treatment works admirably, especially in patients who have been otherwise well treated. It should not, however, be employed in cases of long-standing diabetes in which the patients have been on a liberal diet. Nothing is so likely to throw such patients into dangerous coma as radical treatment.

Students of diabetes have been longing to discover some antiketogenic substance that could be readily oxidized in the body. Although alcohol is such a substance, it has undesirable physiologic effects and cannot be relied upon. It is to be hoped that chemists may soon find the ideal substance. As possibly antiketogenic, mannite (Hirschfeld), xylose (Mohr and Loeb), and inosite, glycerin and glycuric acid (Burr and Blum) have been recommended. Strauss, as already mentioned, recommends inulin.

Carbohydrate is antiketogenic to the extent to which it is burned in the diabetic's body. Because of this fact, some physicians have boldly used dextrose or levulose, and also honey, in the treatment of coma. One hundred grams of levulose may be given intravenously in normal salt solution. I have had no personal experience with this method, and the literature concerning it is too meager to permit of a definite conclusion.

BLOOD TRANSFUSION.—Raulston and Woodyatt applied blood transfusion in severe diabetes. They found that the transfusion of 500 c.c. of peripheral venous blood from a healthy male donor into the peripheral vein of a brother suffering from severe diabetes mellitus had a decided effect on the metabolism of the latter, as evidenced by a marked rise in the output of sugar, ammonia and acetone bodies, and an increase of the glucose-nitrogen ratio. In severe diabetes mellitus blood transfusion is therefore definitely contra-indicated.

SURGICAL TREATMENT

Several surgeons (Robson, J. M. Hutcheson) have suggested that cases of diabetes be submitted to surgical treatment, especially when a pancreatic origin of the disease seems likely. The following are Robson's conclusions:

1. The early recognition and treatment of interstitial pancreatitis or of pancreatic catarrh by drainage of the bile ducts, and thus indirectly of the pancreatic ducts, and removal of the cause, whether that be gall stones, duodenal ulcer, or other conditions, may be the means of averting diabetes.

2. In certain diseases of the pancreas, even after the appearance of glycosuria, surgical treatment is well worth considering, as in a number of cases it has led to a complete disappearance of sugar from the urine and in others to an arrest of the disease causing glycosuria.

3. Every case of diabetes should be considered from its etiological point of view, seeing that certain cases of glycosuria of pancreatic origin are curable, and in others the progress of the disease may be arrested by suitable surgical methods that can be carried out with very small risk.

In my own experience there have been few cases in which either the history or the associated conditions suggested a definite disease in the pancreatohepatic area.

DRUGS IN DIABETES

The curability of a disease is usually in inverse ratio to the number of remedies suggested for it. In a work on therapeutics on my desk I find forty-three drugs and preparations recommended for diabetes. Those who have had the largest experience with the disease have the least faith in the power of drugs to cure it. The manufacturers of proprietary preparations often make extravagant claims that are not borne out by tests on large series of cases. Success during the administration of a remedy does not prove that the remedy brought about the good result, but may be due to adherence to a correct dietetic regimen, which the literature accompanying proprietary remedies often enjoins. In the following paragraphs I will mention a few of the drugs that have been employed in diabetes, and which in certain instances may do good.

Opium is one of the oldest remedies in diabetes. It seems to lessen the excretion of sugar and slightly to increase the tolerance for carbohydrates. It is especially recommended for driving final traces of sugar out of the urine, but it must be given in large doses, which diabetic patients seem to bear very well. The dose of powdered opium (*pulvis opii*) is 0.06 to 0.18 gram (one to three grains) three times a day. Instead of opium *codein* may be employed, though it is questionable whether it possesses all the properties of opium; but it has the advantage

of being easily administered and being less constipating than the parent substance. It is used in doses of 0.015 to 0.06 gram ($\frac{1}{4}$ to 1 grain) three times a day.

Quite recently *pantopon*, which is supposed to represent all the alkaloïds of opium, has been introduced into the therapy of diabetes. It is given in doses of 0.02 to 0.06 gram ($\frac{1}{3}$ to 1 grain) three times a day.

Arsenic.—The use of arsenic in diabetes is purely empirical, and the evidences of its efficacy slight. Von Noorden in two instances obtained apparently brilliant results with hypodermic injections of sodium arsenate. In eight other cases the remedy failed entirely. Sodium cacodylate has been recommended by Renaut. It may be given hypodermically in doses from 0.03 to 0.12 gram ($\frac{1}{2}$ to 2 grains).

Atropin.—Rudisch and Forchheimer have claimed that atropin increases carbohydrate tolerance. Usually atropin sulphate has been employed, sometimes atropin methyl-bromid. My own experience with both of these salts has been as unsatisfactory as that of Mosenthal, who in a careful study which he made of two cases found atropin sulphate to have no value.

Magnesium Perhydrol.—Rather strong claims have been made for this preparation. Axenberger found that the sugar elimination, the quantity, and the specific gravity of the urine were greatly reduced. The reaction soon became neutral or feebly alkaline, and an existing acidosis disappeared. Stuermer, with a special diet, claims to have secured a reduction in sugar elimination by means of the drug. The dose is 0.5 gram ($7\frac{1}{2}$ grains) three times a day.

The *salicylates* are much employed in diabetes—in the form either of sodium salicylate, 0.3-0.6 gram (5 to 10 grains), or of aspirin in the same doses. While they have no power to do the slightest good independently of dietetic treatment, patients with a certain degree of tolerance (60 to 150 grams bread) sometimes seem to have their tolerance raised while taking them.

Eserin.—Eserin has been used in the belief that as a stimulant to the vagus nerve it would exercise some influence on the organs concerned in the carbohydrate metabolism, but no good effects have been obtained with it. It is a constituent of the valueless proprietary preparation called Diabeteserin.

Lithium carbonate and *lithium citrate* have been used in the diabetes of persons having a gouty taint. The dose is 0.5 gram ($7\frac{1}{2}$ grains).

Uranium nitrate has been given in diabetes. It is capable of reducing the glycosuria, but it accomplishes this, in all probability, by irritating the kidneys and lessening their permeability for sugar.

Syzygium Jambulanum.—Without a regulation of the diet jambul, employed in the form of an infusion of the dried fruit, is useless. With a restricted diet von Noorden found it in a few instances to lessen the

sugar output to the extent of from 15 to 20 grams per day. The drug is, however, now seldom used.

Organic Extracts. Opothepy.—The experiments of von Mering and Minkowski, showing that pancreatectomy in dogs is followed by diabetes, and the pathological studies of the pancreas in human diabetes, have led to the use of dry and fresh pancreas and pancreatic extracts in the treatment of the disease. The results have been disappointing. It is highly probable that the pancreatic ferments and the obscure internal secretion if they exist in the dead gland at all are destroyed by gastric digestion. With this thought in mind I have prescribed pancreatic extract in the so-called glutoid capsules without obtaining any influence on the glycosuria. In only one instance have I seen distinct benefit from pancreatic extract. The patient was a middle-aged diabetic suffering from frequent attacks of pain in the upper abdomen. There were no definite signs pointing to any special organ, but their location led me to suspect that the pain was of pancreatic origin. It was not severe enough to suggest stone. Under the use of pancreatic extract in five-grain doses three times a day the pain invariably subsided very shortly.

A few years ago Zuelzer recommended a "hormone" extracted from the pancreas. It is administered intravenously. Subsequent experimenters (Forschbach) found that the substance produced a pronounced febrile reaction with alarming symptoms of prostration, and warned against its use.

Sewall, using the work of Cohnheim as a basis, employed combined infusion of beef and pancreas as well as beef juice alone in the treatment of diabetes. The beef juice is prepared as follows: One pound of lean beef is ground in a sausage machine, then covered with a pint of cold water to which thirty drops of dilute hydrochloric acid are added. The mixture is allowed to stand in the ice box all night or at room temperature four hours, and is then strained through cheese cloth. The liquid should be drunk in the course of a day, one-half to one tumblerful at a time.

The mixed beef and pancreas infusion is prepared in the following way: Six ounces of ground fresh pancreas are soaked all night in a quart of water acidulated with a dram of dilute hydrochloric acid. After straining a pound of ground beef is added to the fluid. After remaining at room temperature for four hours, the mixture is again strained and the juice then consumed by the patient in the course of twenty-four hours.

Sewall found the acidulated beef infusion to be of some value in the diabetes of the aged. Barring temporary benefit in a single case, the combined pancreas and beef infusion had no noticeable effects.

Secretin.—This is a substance prepared by extracting duodenal mucosa. It has been used in diabetes, chiefly in England. The results have not been encouraging (Bainbridge and Badder), although Moore, Eddy,

and Abram report good effects. *A priori* one would hardly expect secretin to be of any value, since it is a hormone stimulating the external secretion of the pancreas.

Yeast.—Yeast has been recommended on the ground that its ferment zymase is glycolytic and breaks up the sugar into intermediary compounds which the diabetic is able to utilize. It is a question, however, whether the sugar decomposes in the body in the same manner as in the test tube. Nor is it known whether the enzyme unfolds its activity only in the alimentary canal or whether it can act on the sugar after absorption. Aside from the ordinary brewer's yeast various yeast extracts have been employed. These extracts are, to a considerable extent, of proprietary nature and need not be specially mentioned here. One of the proprietary ones is highly praised by Seemann, but when his figures are studied the results are by no means striking. Fränkel found tablets prepared from yeast zymase useful in diabetes.

Another proprietary preparation, called "Fermocyl," and composed of the invertin of yeast cells and the amylase of the pancreas, has been recommended by Schnée. Its value is most problematic.

Trypsogen.—This is a substance prepared from the tails of the pancreatic glands of young animals, for which the makers claim that it contains the "enzymes of the islands of Langerhans, the tryptic, amyloptic ferments." The tablets on the market also contain gold bromid, .01 grain, and arsenic bromid, .02 grain. The dose is from two to eight tablets, three times a day. The manufacturers state that trypsinogen has the same action as Zuelzer's pancreatic hormone, concerning the utility of which there is, however, grave doubt. Aside from the fact that little if anything is known regarding the ferments of the islands of Langerhans in contradistinction to those of the acini, it is doubtful whether the enzymes present in the preparation, and which act only in alkaline media, can withstand the action of the acid gastric juice.

Lactic Acid Bacilli.—Lactic acid bacilli have been recommended for nearly every ill that flesh is heir to, including diabetes (Horowitz). The drug manufacturers have not been slow in seizing the psychological moment and putting upon the market innumerable preparations containing various strains of these bacilli. Quite recently the Bulgarian bacillus has been proposed as a remedy for diabetes, but so far no scientific study of the subject has appeared; moreover, it is *a priori* unlikely that it will have any special virtue in the curing of the disease.

HYDROTHERAPY

The ordinary bathing to which the patient is accustomed may be continued without change except in the case of cold plunges. In the diabetic who is losing weight cold bathing is not only a shock to the system, but

brings about an unnecessary increase in the energy requirement. Cold sponging suffices, and even that is inadvisable when there are acidosis and rapid emaciation. Diabetic patients with strongly marked neurasthenia—a frequent occurrence—are benefited by warm, prolonged bathing either in plain water or in water charged with carbon dioxid. Sea bathing is not an indifferent procedure for diabetes and the question of its advisability must be carefully weighed in every case. Those that are highly neurasthenic ought to abstain from it, for they become quickly fatigued and depressed after an ocean bath. For a robust diabetic, in weight equilibrium, a short ocean bath is probably not harmful.

HEALTH RESORTS FOR DIABETICS

A number of places, chiefly on the continent of Europe, enjoy a reputation in the treatment of diabetes. It is an open question whether there is anything in the climate, in the baths, or in the drinking water of any of these resorts that has a particular influence on the disease; yet there must be something in the treatment at Carlsbad, Neuenahr, Vichy, and other famous spas or diabetics would not go there year after year by the thousands. The good effects of Carlsbad, for example, cannot be disputed. And it has been the experience of a number of observers that they cannot be duplicated by drinking the Carlsbad waters at home, even if the temperature of the water is raised to that of the springs. The quiet, peaceful life, beautiful scenery, and well-prepared food are no doubt factors in the good effects. Another very important thing is the knowledge of the disease and its dietetic treatment possessed by the physicians in Carlsbad and other places much frequented by diabetics. Whether the presence of radio-active emanations, as is claimed by some Carlsbad physicians, plays a therapeutic rôle is still an unsettled question.

In the diabetes of childhood and advanced age but little benefit is to be derived from watering places. Carlsbad and Marienbad are certainly contra-indicated. Good results may at times be obtained at Neuenahr, Vichy, and Homburg. A tendency to diarrhea contra-indicates Carlsbad, Kissingen, and Homburg. No patient in a state of rapid emaciation should be sent to a spa. When there is marked albuminuria Marienbad and Carlsbad are not suitable. Neuenahr, Vichy, Homburg, and Wiesbaden are better in such circumstances. Cardiovascular disease contra-indicates Carlsbad, Vichy, and Neuenahr. Benefit may be derived from hydrotherapeutic treatment at Homburg, Kissingen, Marienbad, and Nauheim. Anemia contra-indicates Carlsbad and Neuenahr. For such cases von Noorden recommends ferruginous baths and mountain climate. Old persons do better in the warm seashore resorts in the winter; in this country Florida, Southern California, and even Atlantic City for short sojourns; in Europe the Riviera. For children and young adults

strong drink cures are not to be employed; sea baths, salt baths, and altitude resorts are best adapted.

EXERCISE IN DIABETES

The treatment of diabetes with muscular exercise is based on the investigations of Külz and von Mering, who showed experimentally that muscular movements diminish sugar elimination. Previous to Külz, Trousseau and Bouchardat discovered the same fact by clinical observation. More recently Allen has shown that exercise is useful not only in the vigorous diabetic, but also in the weak. Barringer and Moriarta have also pointed out the value of exercise in diabetes. Exercises should take the form of walking, mountain climbing, dumb-bell and Indian-club practice, mild tennis, and bowling. Horseback riding is also beneficial, especially for those with sedentary occupations. The effect of massage is analogous to that of muscular work. In severe cases, especially in those with acetonuria, active exercise is contra-indicated.

TREATMENT OF SPECIAL SYMPTOMS

Care of the Teeth.—Mention has already been made of the tendency in diabetes to pyorrhea alveolaris. The teeth of diabetics seem also liable to early caries. The danger of infection through decayed teeth and through the gums in pyorrhea must be combated by scrupulous care of the mouth on the part of the patient and the dentist. Pyorrhea, even when extensive, is no warrant for the immediate removal of the teeth. In one diabetic patient whose teeth were nearly all loose, treatment by a skillful dentist cured the pyorrhea completely. Whenever it is necessary that the teeth be drawn a general anesthetic should not be used.

Itching.—This is sometimes intolerable, and if the itching is in the region of the vulva, anus, or scrotum the skill of the physician is often taxed to its limit to provide relief. I have seen a case of pruritus of the scrotum of such intensity that the patient harbored thoughts of suicide. If the itching is general relief may at times be obtained from prolonged warm soda baths containing from four to five ounces of washing soda to twenty gallons of water. In some cases the addition of a pound of starch may add to the soothing qualities of the bath. Of local applications, those containing phenol, menthol, or thymol may be employed. Phenol may be used in the strength of 4.0-8.0 gm. (one or two drams) to the pint of water, menthol in strengths of 2.0-3.0 gm. to 500 c.c. (thirty to forty-five grains to the pint) with a little alcohol and glycerin. Ammonia water of moderate strength is also useful. Crocker advises the following:

- R Thymol, 15 gm. (3iv).
Liq. potassæ, 8 gm. (3ii).
Glycerin, 24.0 c.c. (3vi).
Water, q.s. ad 500 c.c. (one pint).
M. S.—Local use.

I have seen benefit from the calamin lotion. When the skin is dry and scaly, ointments are preferable to lotions. The following is recommended by Schamberg:

- R Menthol, 0.6-1.3 (gr. x-xx).
Pulv. camphoræ, 1.3-2.0 (gr. xx-xxx).
Phenol, 1.3-2.0 (gr. xx-xxx).
Adipis benzoat., 60 (3ii).
M. S.—Local use.

Aside from the measures just mentioned, I found in one instance that an obstinate pruritus vulvæ disappeared on the application of brewer's yeast. In pruritus of the scrotum a well-fitting suspensory should be worn. In pruritus an ointment of calomel, twenty grains to the ounce of petrolatum, or cold cream, or one of phenol, may be used. The brilliant results achieved by the X-ray in dermatology justify a trial of it in the local forms of pruritus met with in diabetes, especially in pruritus vulvæ.

Boils.—Boils are quite frequent in young and middle-aged diabetics. Occasionally one meets an individual whose urine is free from sugar during a siege of boils, but gives the glucose test soon afterward. The local treatment consists in the use of Bier's hyperemia cup and, failing in this, in incising the boil as soon as evidences of suppuration are present. If the boil is very painful and shows no sign of coming to a head, one of the best applications is a flaxseed poultice made with a one to two thousand bichlorid of mercury solution. The internal administration of brewer's yeast in doses of one or two teaspoonfuls three times a day has been much used in the treatment of boils. Various extracts of yeast are on the market, designed to obviate the disagreeableness of the native remedy. If the boils persist in spite of the usual forms of treatment, recourse may be had to vaccines, the autogenous vaccines being the best.

Sodium phosphate, sodium arsenate, and calcium sulphid have been recommended as useful in the preventive treatment of boils in diabetes.

Xanthoma Diabeticorum.—This skin affection, first described by Crocker, is most common in young adults; it is not of serious moment and usually yields to ordinary antidiabetic treatment.

Diabetic Vulvitis.—Cleanliness, douching several times daily with hot salt solution, and afterwards drying the parts carefully with a soft

towel are useful measures. Vaginal irrigation, once daily, with a solution of corrosive sublimate, one to two thousand; creolin, 1 per cent., followed by an ointment of salicylic acid, 0.6 to 30 gm. (ten grains to one ounce) of petrolatum; or dusting powders, equal amounts of calomel and bismuth subnitrate or oxid of zinc, may be prescribed. Excoriations and abrasions should be painted occasionally with nitrate of silver, 1.5 to 30 c.c. (twenty grains to the ounce); benzoated oxid of zinc ointment containing 3 per cent. of phenol, or an ointment of petrolatum containing 20 per cent. oxid of zinc may then be applied.

Diabetic Neuralgia.—Neuralgia involving the trifacial nerve, either all the branches or only one of them, most often the dental, is not infrequent in diabetes. The presence of such a cause should therefore be borne in mind and the urine examined in all cases of neuralgia. The principal aim should be the lessening of the hyperglycemia by diet. For the attack the various anodynes, such as antipyrin, 0.3 to 0.6 gm. (five to ten grains), acetphenetidin, 0.3 to 1.0 gm. (five to fifteen grains), pyramidon, 0.3 to 0.5 gm. (three to seven and a half grains), etc., may be used; or the high frequency current, and in rebellious cases alcohol injections.

Excision of the Gasserian ganglion is such a formidable operation even in nondiabetic subjects that it is only justifiable in extreme cases and under full realization of the danger of coma.

Brachial Neuritis.—This, painful enough under ordinary circumstances, becomes a terrible torture in diabetic patients. It is usually unilateral, but may be bilateral.

Proper diet must be instituted and the patient must have mental rest, sometimes even physical rest. Hot applications in the form of hot wet compresses and electric light treatment are useful. In recalcitrant cases a trip to Carlsbad may be advised.

Sciatic Pain.—Pain in the course of the sciatic nerve is very common in diabetes. It is usually bilateral. It may affect the entire nerve or may be referred particularly to the calf. In all cases of bilateral sciatic pain the urine should be examined for sugar. Sometimes the symptoms are suggestive of locomotor ataxia, the pains being of a lightning-like character. The knee-jerk, you will note, is at the same time absent.

Here, too, the principal treatment is that of the diabetes, together with rest in bed and the use of one of the various coal-tar preparations of which several have been mentioned above. In severe cases I have thought that some relief was obtained from methylene blue, given in pill form in doses of 0.06 gm. (one grain), usually with a little extract of belladonna, 0.005 gm. (1-12 grain).

Impotence.—This may be a very early symptom of diabetes. As a general rule, the prognosis for restoration of function is not good. Drugs

have little value if antidiabetic diet fails. I have seen no benefit from the much vaunted yohimbin.

Prostatic Disease.—This complication, to which Heinrich Stern has called special attention, is not common, but should nevertheless be recognized. It will not improve under local therapy unless proper antidiabetic treatment is applied. The prostatic symptom-complex may occur much earlier in the diabetic than in the normal individual.

Diabetic Eye Affections.—The most important are cataract and retinitis. There seems to be no relation between the cataractous condition and the type of the diabetes, amount of sugar, or general state of the patient's health. In considering operation the danger of coma must be borne in mind.

Diabetic retinitis demands general dietetic treatment and rest of the eyes.

Hemorrhages into the several parts of the eye—conjunctiva, vitreous, and sclerotic—occur; also various disturbances of refraction and accommodation—all must be treated jointly by the ophthalmologist and the clinician skilled in the dietetic treatment of the underlying disease.

Diabetic Gangrene.—A good deal can be accomplished by conservative treatment. Stetten advocates the use of hot bathing with sterile physiologic salt solution at a temperature of about 110° F. for half an hour twice daily. If possible, the entire limb should be immersed. Instead of this, the limb, after careful wrapping, may be exposed to hot air in an electric oven. The exposure should not last more than half an hour, and the temperature should not exceed 200° F. Local infections must be treated by the most careful methods of asepsis and antisepsis. When operation is necessary, amputation is to be preferred to arteriovenous anastomosis (Stetten).

The whole subject of diabetic gangrene is discussed in an interesting symposium by Kraus, Payr, Naunyn, von Noorden, Minkowski and Karewski.

DIABETES IN CHILDREN

As a general rule, diabetes in children is a very serious disease. There are, however, mild cases, as has been pointed out by Salomonson and by Riesman. These in some respects partake of the nature of renal diabetes, and are not difficult to manage satisfactorily. But even in severe cases improvement, if not cure, is sometimes obtainable. For this reason the prognosis should be guarded, but not hopeless.

The treatment does not differ materially from that of diabetes in adults. Children bear fasting well. The carbohydrate allowance, when once the diet has been established, should always be less than the tolerance. A child that has been diabetic should never be allowed to take sugar in any form. Meats, eggs, vegetables and fruits of the five and

ten per cent. groups, cream, butter, cheese and nuts, in proper proportion, constitute the dietary. Gluten and other breads are best forbidden; but, if necessary, a bran bread made of bran, agar and salt, as recommended by Allen, may be permitted. Saccharin is not good for children.

Diabetic children, if the disease is at all severe, should be taken from school, and should not be allowed to take part in energetic play. During the summer, the seashore is more suitable for them than the mountains.

In the acidosis of children Langstein recommends fat-poor buttermilk.

DIABETES IN THE AGED

On taking charge of elderly diabetic patients one should scrupulously avoid all radical procedures. If the diabetes is not causing any distress, it is unwise to change the established habits of the patient, even if they are such that they do not comport with one's scientific notions in regard to the proper treatment of diabetes. If changes are made, they should be made gradually, and in no circumstances should the fasting treatment be rudely instituted. It takes very little, even in a patient who is not showing any signs of acidosis, to precipitate an attack of coma. Especial care is necessary in the event of even trivial illness or accident. In short, it is more important to treat the patient than to treat the disease.

DIABETES IN PREGNANCY

Felix Hirschfeld finds that diabetes not rarely gets worse in the third or fourth month of pregnancy, the acidosis being more affected than the glycosuria. Nevertheless, neither during pregnancy nor during the puerperium is coma likely to occur. In general the prognosis is relatively good, especially as the scant diet after labor may bring about a disappearance of the sugar. About ten per cent. of pregnant nondiabetic women show glycosuria during pregnancy, either by reason of a predisposition to diabetes or because of nervous disturbances. Hirschfeld is inclined to look upon these glycosurias, as well as upon alimentary glycosuria in pregnancy, as an expression of a mild diabetic disorder of metabolism. It is mild even if diacetic acid transiently appears. The pregnant diabetic woman should be carefully watched throughout the pregnancy and afterwards. There appears to be no danger whatever to the child from being nursed by its diabetic mother, but lactation should be interrupted if it proves too great a drain on the mother's system.

The treatment of the diabetic during pregnancy is not different from that in other circumstances. Acidosis requires prompt attention. If labor promises to be protracted, the advisability of Cesarean section should be considered. As already stated, the preferable anesthetic is nitrous oxid gas and oxygen.

COMPLICATIONS OF DIABETES

DIABETES AND TUBERCULOSIS

Von Noorden found tuberculosis in 29 out of 252 cases of diabetes, or in about 12 per cent.; Williamson, in 20 out of 100 consecutive cases; Montgomery, in 138 out of 355 autopsies (38.9 per cent.).

It is important to bear in mind that tuberculosis may exist for a long time in the diabetic patient without manifesting itself by characteristic symptoms. In some instances the tuberculosis undoubtedly antedates the diabetes. In the reverse case, which is the more common, the tuberculosis usually runs a rapid course.¹

In the treatment of combined diabetes and tuberculosis one must be governed by the dominant disease. Sanatorium treatment in a mild climate is advisable. The diet must be determined in each individual case. If the pulmonary process is in its incipient stages, the attempt should be made, other things being favorable, to render the patient sugar-free as promptly as possible, and then to build up a protein-fat-carbohydrate diet that will produce a nearly normal caloric intake.

DIABETES AND ARTERIOSCLEROSIS

The majority of middle-aged diabetic patients show arteriosclerosis with hypertension. According to Elliott, and Janeway, the diabetes is not the causative agent in the arteriosclerosis; but I myself rather incline to the view that, for some reason or other, diabetes causes an earlier development of arteriosclerosis.

Treatment.—The ordinary diet for cases of mild diabetes is too rich in protein, and probably in purins. It is, therefore, advisable to lessen the meats and meat broths, and also to eliminate entirely the condiments and sauces. The vegetables and the allowed fruits must be increased, and perhaps also the milk, keeping in mind always the desideratum of no sugar in the urine. If the hypertension produces symptoms,—vertigo, headache, cardiac discomfort,—the nitrites and the iodids are indicated; also electrotherapy and venesection.

DIABETES AND NEPHRITIS

Nephritis is a common development in long-standing cases of diabetes, although it usually does not materially influence the course of the

¹There have come under my observation the cases of two physicians who had diabetes and tuberculosis. Both men had been serving in the same hospital, in which they had been exposed to tuberculous infection. One died as the result of hemoptysis; the other, of exhaustion due to a progressive tuberculosis of the lung.

disease. As already mentioned, it may lessen the glycosuria without diminishing the hyperglycemia. It may lead to a true uremic coma, which, in the circumstances, may readily be mistaken for diabetic coma. In cases in which the nephritis assumes prominence, a certain amount of protein restriction is necessary. The principles governing these cases are very much the same as those mentioned in connection with arteriosclerosis.

ANGINA PECTORIS

Angina pectoris, occurring in the course of diabetes, of which I have seen a few examples, requires no treatment different from that employed when it is not so associated.

DIABETES AND SYPHILIS

As a cause of diabetes syphilis does not occupy an important place, although Warthin and Wilson (*loc. cit.*) find that the association of the two, especially syphilitic disease of the pancreas with diabetes, is not rare. Perhaps if the Wassermann test be made in all cases of diabetes, syphilis will be more frequently detected.

The salient point is that there is danger in mercurial treatment; for not alone is stomatitis, if it occurs, likely to take a severe form, but gangrene may ensue, and if tuberculosis exists it may take a more rapid course (Falta). It may therefore be advisable, in otherwise suitable cases, to use salvarsan by the intravenous method. If mercury is employed its effects should be carefully watched.

DIABETES AND THE THYROID GLAND

As has been previously stated, the thyroid gland has a share in carbohydrate metabolism by exercising an inhibitory influence on the pancreas. I believe, however, that the diabetogenic power of the thyroid has been overestimated. In my own experience the two diseases—diabetes and exophthalmic goiter—have been very rarely associated. I have also seen persons take large quantities of thyroid preparations without becoming glycosuric.

When the two diseases coexist treatment is complicated, for proteins, which are generally used in considerable quantity in diabetes, have an irritative effect on the thyroid gland. Moreover, surgical treatment of the goiter is rendered more dangerous by reason of the presence of diabetes. The X-ray has proved of some value in the treatment of thyrogenic diabetes. In many cases it has failed; and the success or failure of the treatment seems to depend upon whether the thyroid is or is not the chief factor in the diabetes. Schwarz and Hirsch have observed the disappearance of alimentary glycosuria under the use of the X-ray in Basedow's disease.

SURGICAL OPERATIONS IN DIABETIC PATIENTS

The exaggerated fear of clinicians and surgeons of operations on diabetic patients is rapidly giving place to a more aggressive attitude; one recent writer goes so far as to say that the indications for surgical interference in the diabetic are not materially different from those in the non-diabetic. I am, however, of the opinion that all operations that can be avoided in diabetic subjects should be avoided, especially those requiring general anesthesia. Narcosis merely for diagnostic purposes is not justified. Confronted with an emergency such as strangulation of the bowels, acute appendicitis, severe injuries, etc., the same course should be pursued as if the patient were not diabetic. Preceding all operations that are not of an emergency character an attempt should be made to render the urine sugar-free. Whether the patient should be treated by the Allen method before operation or by the method of gradual carbohydrate withdrawal and a protein-fat diet, has been a matter of dispute among surgeons. Some authorities (Jopson, Meeting of the Medical Society of the State of Pennsylvania, September, 1916) are opposed to the Allen method, while others (Behrend, the same meeting) advocate it. Whether the method should or should not be used in such circumstances must be determined on the same principles as are applicable to nonsurgical cases.

It is not absolutely necessary that the last trace of sugar should be banished before undertaking an operation that is important for the life or the comfort of the patient; particularly does this hold good if the patient's general health is satisfactory and if diacetic acid is absent from the urine. A diabetic woman under my care required an operation for an extensive perineal tear. When she entered the hospital her urine contained a large percentage of sugar. Under strict diet she became almost, but not quite, sugar-free. The operation was not followed by any untoward symptoms, recovery was prompt, pregnancy ensued, and a healthy child was born at term.

It is well to administer alkalis before an operation whether diacetic acid is or is not present in the urine. If there is acidosis the dangers of an operation are greatly enhanced, and unless it is of an emergency character, the operation should be postponed and an effort made to lessen or abolish the ketonuria. In addition to pushing the alkalis before and after operation, a liter of a 5 per cent. solution of sodium bicarbonate should be introduced into a vein while the patient is still under the influence of the anesthetic.

The co-existence of arteriosclerosis with diabetes increases the hazard of an operation, as do all serious conditions affecting the heart and kidneys. On account of the liability to septic infection it is important to minimize tissue trauma. Ether is a safer anesthetic for the diabetic than chloroform, but whenever possible local anesthesia should be em-

ployed. Where a skilled anesthetizer and the necessary apparatus are available nitrous-oxid-oxygen anesthesia is the best, even for prolonged operations. In proper hands spinal anesthesia is preferable to general narcosis. Operations requiring general anesthesia should be performed early in the morning, as protracted fasting before the operation may be harmful to the patient.

In local anesthesia too much fluid should not be introduced, as great tension of the tissues may lead to sloughing.

From a surgical point of view all cases having sugar in the urine, whatever the cause, should be looked upon as diabetic, and all of the precautions mentioned above should be taken. The glycosurias associated with injuries, especially cerebral injuries, usually disappear after operation. Nevertheless it is advisable, as recommended by Kausch (30), to make the alimentary test before the final discharge of such patients. If the response is positive the patient may become diabetic and should be kept under supervision.

Effect of Surgical Operations on Diabetes.—Diabetes sometimes disappears after surgical operations, especially after prostatectomy and hysterectomy. (Eising, Manges—quoted by Eising,—Joslin, and Miller.) I have seen sugar disappear after hysterectomy for fibroid tumor and after drainage of an appendiceal abscess.

DIABETOPHOBIA

A morbid fear of diabetes is easily roused in many intelligent persons, especially those in whose families diabetes has existed. The physician should be careful in expressing an opinion until he has assured himself that the reducing substance in the urine is sugar and, as already stated, before declaring a patient diabetic he should make sure that the glucose found is not due to an inordinate intake of sugar. I have in mind a young man who has become morbid over a disease which is in a very mild form, because a medical friend of his made the remark that young diabetics were sure to die early of their disease.

MAY DIABETICS MARRY?

Young persons with pronounced diabetes ought not to marry, as the duration of life for them is, as a rule, not long. It is probable that the nervous excitement attending a honeymoon as well as the difficulty in carrying out the proper regimen increases the danger of acidosis and coma. Moreover, diabetes may in many cases lead to early sterility and impotence.

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CHAPTER V

DIABETES INSIPIDUS

DAVID RIESMAN

[REVISED BY KETIL MOTZFELDT]

Diabetes insipidus is a disease in which there is a permanent elimination of an excessively large quantity of sugar-free urine of low specific gravity without demonstrable lesion of the kidney. Two ways are conceivable in which the cardinal symptom of the disease may be brought about: there may be a primary polyuria with a secondary polydipsia or the reverse, a primary polydipsia with a consequential polyuria. In practice it may be difficult to determine to which type a given case belongs. There are undoubtedly cases in which the primary fault is an intense thirst—these are usually instances of functional nervous disease, hysteria, etc. Such patients pass large amounts of urine because they have acquired the habit of excessive water drinking. The other group, the primary polyurias, includes the majority of cases of diabetes insipidus. Here the fault is not excessive thirst, but inability on the part of the kidney to excrete a urine of proper concentration. Having lost the power of concentrating the urine in a normal manner the kidney, in order to rid the system of the daily quota of solids, must excrete a larger amount of dilute urine. As a result of this enforced polyuria the total solids eliminated reach the normal; at the same time abnormal constituents such as sugar or albumin do not appear.

The condition must not be confounded with chronic interstitial nephritis nor with arteriosclerotic hypertension. Cardiac hypertrophy, arteriosclerosis, and high blood pressure are absent from the clinical picture of true diabetes insipidus.

Whether a given case belongs to the group of primary polyurias can usually be determined by the sodium chlorid test. When a normal individual on a standard diet containing a definite quantity of sodium chlorid receives an addition of from 10 to 15 grams of NaCl to the daily

ration the sodium chlorid concentration in the urine increases, while the urine quantity varies little or not at all. In a patient with diabetes insipidus, on the other hand, with a similar experiment, the sodium chlorid concentration of the urine is only slightly affected, but in order to get rid of the excess of salt the quantity of urine excreted is greatly augmented.

It should be remembered, however, in this connection that the concentration of the urine cannot be accurately determined by the estimation of the NaCl; the best method is the determination of the freezing point (Δ).

As these facts are important from the standpoint of treatment I reproduce two tables from a valuable article by Erich Mayer:

TABLE I

Behavior of an individual with healthy kidneys on the addition of a single quantity of NaCl to a standard diet.

Quantity of Urine	Spec. Grav.	Δ	NaCl %	NaCl Grams	N %	N Grams
1375	1011	0.78	0.198	2.72	0.803	11.04
1200 (10 gm. NaCl)	1011	0.91	0.444	5.33	0.890	10.70
1700	1012	0.88	0.374	6.36	0.704	11.97
1450	1010	0.75	0.316	4.48	0.570	8.28

TABLE II

Elimination in a case of diabetes insipidus in which, in addition to a diet containing about 9 grams NaCl, 10 grams NaCl dissolved in 15 c.c. water were given through a stomach tube.

	Urine Quantity	Spec. Grav.	Δ	NaCl %	NaCl Grams	N Grams	λ
Preliminary day	7650 c. c.	1004.800	0.23	0.117	8.95	11.78	0.003346
10 _g NaCl	10600 "	1004.202	0.20	0.176	18.76	11.13	0.004535
Succeeding day	7850 "	1003.078	0.20	0.105	8.24	11.69	0.002550

Δ —Freezing point of urine.
 λ —Electric conductivity.

Treatment.—In the cases of secondary polyuria associated with functional nervous disease a restriction of the water intake may at times be achieved by psychotherapy. As sleep is much disturbed by thirst and the necessity for passing water, benefit may be derived from the administration of bromids and mild hypnotics. The use of chewing gum, slippery elm, etc., may, by allaying the dryness of the mouth, lessen the craving for water.

In the primary cases the treatment is chiefly dietetic. The NaCl test

shows us the way. Since the addition of salt increases the polyuria a salt-poor diet is indicated. The quantity of urine does not, however, depend solely on the amount of salt to be excreted—but rather upon the total number of nitrogenous and nonnitrogenous molecules of waste to be eliminated. Hence a diet containing a minimal quantity of urinary waste material is best calculated to reduce the polyuria. Such a diet would be made up of green vegetables, fruit, puddings, pastry, unsalted bread, unsalted butter, and meat without salt. As carbohydrates and fats are well borne free use may be made of them.

Most of the animal foods are poor in salt, and as the proteids do not affect the polyuria to the same extent as salt they are allowable in moderation. A mixed diet containing only 5 or 6 grams of NaCl may be kept up indefinitely without injuring the health of the patient. On such a diet from 3 to 5 liters of urine are excreted in the average case. Instead of salt, mustard, pepper, and other condiments, forbidden in nephritis, may be used. Care should be exercised that as little fluid as possible is taken during the late afternoon and evening, as that makes for less disturbed nights. The more concentrated foods should be incorporated in the meals of the first half of the day.

During recent years our knowledge of the etiological factors in diabetes insipidus has been considerably advanced. These conceptions have already been reflected in the treatment, which at present seems to be more promising than previously has been the case.

Previous observations had shown that bitemporal hemianopsia was a frequent complication in diabetes insipidus and it has been a well-established fact that syphilis very often was noted. The frequent connection between diabetes insipidus and trauma of the skull and organic diseases of the brain had also been observed.

The explanation of these facts is due to the rapid development of our understanding of the ductless glands, and in particular of the pituitary body. During the past three or four years many cases have been reported, where the relationship between diabetes insipidus and diseases of the pituitary body is unquestionable. In most of these cases the autopsies have revealed tumors of various kinds, of the hypophysis, or syphilitic or tuberculous lesions of the gland.

Combinations of diabetes insipidus with universal adiposity, infantilism or somnolence have also been seen, and reviewing the literature on the subject, it is found that underdevelopment, drowsiness, subnormal temperature, anhidrosis, amenorrhea and impotency are known to be common symptoms. These are some of the most important manifestations of hypofunction of the posterior lobe of the hypophysis. It is, therefore, justifiable to assume that probably a great number of true diabetes insipidus cases, in other words the primary polyurias, are of a pituitary origin.

According to the physiologists the pituitary extracts exert a very marked diuretic effect. These statements have been accepted by the clinicians, and it may be found in almost every textbook dealing with these subjects, as an ascertained fact, that these extracts are "powerful diuretics."

These views have led to considerable confusion and have hampered our conception of the etiology of diabetes insipidus. Later studies, however, have shown that this diuretic effect not only does not exist but that the extracts are able to produce a very marked antidiuretic effect. Injections of extracts made from posterior lobe will invariably decrease the output and concentrate the urine, as well in patients suffering from diabetes insipidus as in normal persons and in animals used for experiment.

Such data, although very new, are sufficient to indicate that treatment with pituitary preparations ought to be tried in every case of primary polyuria. One, or more, subcutaneous injections of the usual commercial extracts from the posterior lobe will probably have a marked influence on the diuresis, but the effect is only temporary and usually does not last longer than twenty-four hours. The injections are well borne; paleness of the face, slight headache and dizziness may, however, occur, lasting only for a few hours. Intravenous injections are not advisable.

Treatment by mouth is far less effective, but as this treatment is without any discomfort and absolutely without danger, even in large doses, it can be kept up for an indefinite period. The sufficient dose has to be ascertained by trial in each case, and usually very large doses are required, since the amount of the active principle, absorbed from the intestinal tract, seems to be very small. Where it is possible the treatment should be carried out with fresh material from the abattoir, as well from economical reasons as from the fact that the fresh material is much more potent than the dried preparations. As it is very difficult, however, to check the twenty-four hour amount in this way, it will probably, in many cases, be the best plan to confine the therapeutic aim to securing a normal output during the night and thus relieve the patient of one of the most distressing features of the disease,—the restless nights.

One patient, who has been under my care for the past two years, has been very much improved by an intermittent pituitary feeding. She has taken from two to seven fresh pituitary bodies from cattle every evening; the output has thereby been checked during the night, usually decreasing from nearly 2,500 c.c. to approximately 300 c.c. At the same time the general state of health has improved, adiposity and drowsiness having disappeared, and menses have been reestablished.

Only the future can tell how many cases will yield to a similar treatment.

A salt-poor diet is a valuable aid in the treatment.

In the syphilitic cases an energetic specific treatment will sometimes prove of lasting value.

Drugs are of little value in the treatment. Strychnin, theocin, ergotin and opium have been recommended, but have not proved very efficacious. The last mentioned drug will often decrease the thirst, and in that way exert influence on the diuresis.

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CHAPTER VII

RACHITIS

ISAAC A. ABT

812. Lines 23-27 *read*:

tions of the city. **It is said that in the City of Berlin 90-98 per cent. of all the children who are examined show some evidence of rickets.** In the far north, the disease is rare; in the south temperate zone it is uncommon. It is rare in the sub-tropical regions. **It is not of frequent occurrence along the southern Italian shores, though in this country, as everybody knows who visits the dispensaries and clinics of our large cities, rachitis among the Italian children is of very frequent occurrence.** The same thing is true for colored children in northern climate, while in the tropics, the negroes are said to be immune to the disease. It is said not to occur in the tropics.

814. Line 37 *read*:

syphilitic children. **Tuberculosis also may pave the way for rachitic processes in the infant.** Children suffering from whooping-cough, measles and

Line 38 *add* after "rachitic.":

It is thought that rickets has a seasonal occurrence; that it is more likely to occur in the spring of the year than any other time. It has been suggested that the reason for this increased prevalence of the disease at this time of the year is due to the fact that children remain indoors the greater part of the winter; they frequently live in insanitary surroundings where they are deprived of fresh air and sunlight, and the feeding is frequently improper.

815. Line 1 *read*:

ment. Kellar **suggests** that children who lived on the shady side of a

Line 29 *read*:

are more severely, rachitic than any other nationality, **and this is entirely independent of the**

817. Line 22 *add* after "value":

That prevention of rickets has received scant consideration in the literature of the last ten years is the opinion of Ernst Schloss of Berlin. The various methods of feeding children have not taken into consideration the prevention of rickets. It must be acknowledged that even with natural feeding rickets occurs. As a matter of fact, however, the rickets which does occur in babies at the maternal breast is less severe, and only occurs during the first few months of life. Schloss thinks that the prophylaxis against rickets is the most important problem of infantile dietetics, and no food should be passed upon as suitable for infant use until it is determined accurately to what extent the frequency and intensity of the ensuing rachitic processes result from its use. It is true, also, that we have no conception how nature heals rickets. We do not know why soft bone becomes calcified, nor do we know why, at a certain period in the life of an individual, the soft spots become hard and calcified.

The calcium metabolism, according to Schloss, is not particularly favorably influenced by the use of phosphorus and cod liver oil, if given alone, whereas, if calcium acetate be added there is a very distinct increase in calcium retention which is favorable for the treatment of rickets. He gave 1.6 g. of calcium acetate per day.

VOLUME III

I. DISEASES OF THE DIGESTIVE SYSTEM

CHAPTER I

DISEASES OF THE MOUTH

LOUIS STARR

1. Line 9 *read*:

floor of the mouth, salivary glands, and general mucous membrane. **A dentist's mirror is useful.** The

3. Line 4 *add* after "pus":

Peridental lesions, particularly those which exist as closed processes such as alveolar abscesses, are frequently the source of infection which involves distant structures, such as joints. General sepsis also may originate from infections of the mouth, and has occasionally been noted in badly infected mouths following operative treatment when too many teeth have been removed at one sitting.

5. Line 35 *add* after "disorders":

Herpes of the lips and face as well as herpes zoster has been frequently observed simultaneously with and following both acute and chronic infections. In herpes zoster lesions of the spinal ganglia have been found, and the evidence at hand indicates that in many instances the cause of herpes is to be sought in infections, which may be either acute and general, or localized and chronic.

13. Line 40 *read*:

ing, but never extending beyond the cavity of the mouth. **The disease was extensively studied by Gilmer in 1906 and its bacteriology demonstrated for him in 1910 by Tunncliffe.** It is not confined to any ages.

14. Line 17 *read*:

sive breath. Next the **lateral and buccal** gingival border about the **bicuspids** becomes intensely injected and rapidly swells, the interdental points of the gum standing out like flasks and bleeding upon the lightest touch.

Line 23 *read*:

appear on the **buccal or labial** surface of the upper gum, the interior aspect of

Lines 38-39 *read*:

restlessness, and, with little alteration in the temperature range, **usually about 101° F.**, a weak pulse, and other evidences of general debility. **Great mental depression and despondency have been often noted.**

15. Line 15 *add* after "dietary":

Gilmer recommends calomel gr. 1-5 four times a day.

Line 43 *read*:

which the ulceration is most marked are removed. **The removal of teeth in this disease is attended with some danger, however, and should not be attempted while the disease is at its height.** After extraction

17. Line 9 *add* after "contagion":

The bacillus fusiformis has been found in the lesions of noma.

26. Line 16 *add* after "oftener":

Treatment by the Röntgen ray and the cautery is of value.

30. Lines 8-9 *read*:

gland **or at any point in the floor of the mouth** and due to bacterial infection, extending from the mouth through the lymphatic vessels. The atrium of infection is usually some slight le-

Line 25 *read*:

Death often results from **edema of the glottis**, extension to the larynx or lungs, or from

Line 29 *read*:

so soon as suppuration begins prompt and thorough surgical measures **with wide deep incisions under the jaw**

CHAPTER II

DISEASES OF THE PHARYNX

BURT R. SHURLY

32. Line 2 *read*:

ford temporary relief. **The use of a stock vaccine when the bacteriology of the prevailing epidemic is known has been suggested.** The diet should be liquid or simple and non-

33. Line 38 *read*:

at **indicated** intervals to relieve mild forms of chronic pharyngitis. A

34. Line 5 *add* after "treatment":

Pharyngitis, secondary to tonsillitis, should be relieved by tonsillectomy.

Lines 14-15 *read*:

mistaken for spasmodic croup **or laryngeal diphtheria** in cases attended by edema of the larynx. Adults **may be** affected. Digital examination of the

39. Line 25 *add* after "tonsils":

The application of powdered salvarsan to the infected zone has been reported of benefit.

CHAPTER III

DISEASES OF THE THROAT AND NOSE

GEORGE E. SHAMBAUGH

ACUTE TONSILLITIS

Acute inflammation of the faucial tonsils is extremely common. The clinical aspect of the condition varies widely in different cases. In its most usual form the tonsils present a more or less marked swelling associated with a congestion not only of the surface of the tonsil showing in the pharynx but also of the mucous membrane immediately surrounding the tonsil. Not infrequently the crypts of the tonsils become filled with plugs of desquamated epithelium, and in severe cases there may occur small areas of necrosis. This condition is known as lacunar or follicular tonsillitis. These forms of tonsillitis are easily recognized by the patient as well as by the physician. The clinical diagnosis of this condition from diphtheria is not always easily made, especially in the early stages. It is important, therefore, to make a bacterial examination as early as possible, since the value of antitoxin in diphtheria is much greater when given early.

There are a great many cases of acute tonsillitis which are not associated with any marked swelling of the tonsillar tissue. In these cases the presence of a characteristic epithelial plug in one or more of the tonsil crypts associated with the congestion over the tonsil makes a diagnosis very easy. In other cases, the absence of epithelial plugs or the failure to detect their presence, especially in the buried type of tonsil where the surface is hidden behind the anterior pillar of the fauces, obscures the diagnosis of acute tonsillitis. Patients will often deny having had attacks of acute tonsillitis but will admit having attacks of sore throat. When such patients are examined during an attack of sore throat, it will usually be found that they are suffering from an attack of acute tonsillitis. On the whole, there appears to be about as many cases of acute tonsillitis which are not recognized as such, as there are cases where the

condition is diagnosed as tonsillitis. This applies as much to adults as to children. In the latter there is often no complaint even of sore throat, and the condition is suspected because of the sudden rise of temperature, for which no other cause can be detected. Where the tonsils are small or of the buried type the local evidence of tonsillar disease is often not easily discerned. It is important to keep these facts clearly in mind especially because of the close relation which is now recognized to exist between acute, subacute or chronic infection of the faucial tonsils and the occurrence of many serious conditions, the result of systemic infection, which call for the disposal of the primary focus in the tonsil. Of the systemic conditions which owe their origin so frequently to attacks of acute tonsillitis, should be mentioned especially acute endocarditis, acute nephritis, and acute articular rheumatism. There are many other conditions, such as enlargement of the thyroid, acute iritis and appendicitis as well as gall bladder infection and the various conditions which were formerly loosely denominated "rheumatism," which in the light of recent clinical studies are often accounted for plausibly as the result of systemic infection secondary to acute tonsillar disease. A systemic infection resulting from an acute attack of tonsillitis is very prone to be repeated by any subsequent recurrence of the tonsillar infection. It is extremely important, therefore, in the treatment of tonsils that these clinical facts should be kept clearly in mind. The treatment of acute tonsillitis includes very often more than the treatment of the acute attack. It should include a careful consideration of the question of prophylaxis against subsequent attacks of tonsillitis.

The treatment of acute tonsillitis is both general and local. The condition is usually quite contagious and it is important where feasible to enforce isolation. In view of the more serious complications, which so frequently follow acute tonsillitis, it is advisable to keep the patient in bed a few days until fever has subsided. Calomel should be given at night followed by a saline cathartic in the morning. Acetyl salicylic acid (aspirin) (in 5-grain doses) repeated every four hours assists a great deal in lowering the temperature and in relieving the associated headaches and muscle pains. Locally some simple gargle should be given. A teaspoonful of bicarbonate of soda in a tumbler full of warm water, or a normal salt solution, is usually all that is required. In the severe cases where the pain in the throat is great, the following gargle containing carbolic acid gives relief:—carbolic acid $\frac{1}{2}$ dram, sulphocarbolate of zinc 2 drams, water 6 oz. This is to be diluted 3 to 5 times with warm water. When the breath is very offensive hydrogen peroxid diluted 3 to 5 times with warm water may be used as a gargle. For local application to the tonsils, a great many agents have been recommended, including strong solutions of silver nitrate and of guaiacol. The discomfort associated with the application of these agents often outweighs any im-

provement which they may bring about. Argyrol in 10 per cent. solution swabbed over the tonsil and by means of a curved cotton applicator, introduced behind the soft palate, is not unpleasant and accomplishes all that any antiseptic application can do. Iodin in the form of Mandel's solution applied to the surface of the tonsil may also be used,—iodin 5 gr., potassium iodid 25 gr., glycerin 1 oz. When the discomfort from the infiltration of the tissues of the neck is very great, the application of a cold compress gives some relief. A cloth is wrung out of ice water and applied around the throat. Over this is placed a piece of oiled silk and about this compress is placed a suitable retaining bandage. The use of ice bags may also increase the comfort of the patient.

Formation of an abscess in the tonsil (quinsy sore throat) or of an abscess in the tissue about the tonsil (peritonsillar abscess) requires in addition to the treatment for acute tonsillitis the surgical opening of the abscess. The formation of an abscess in the tonsil is recognized by the increased swelling of the tonsil, crowding it toward the median line, and by the presence usually of edema of the anterior pillar and uvula. The abscess usually points on the free surface of the tonsil. A peritonsillar abscess forms usually about the apex of the tonsil between the layers of the soft palate. It is especially apt to occur in the type of tonsil where the upper lobe is deeply imbedded. The infiltration is more above the tonsil and causes a diffuse bulging of the soft palate towards the median line. A serious complication of phlegmon of the tonsils is the development of an edematous infiltration of the lateral bands of the pharynx just back of the tonsils. This edema tends to extend downward and may produce edema of the glottis, necessitating intubation or tracheotomy.

The incision for opening an abscess in the tonsil is made toward the base of the tonsil. The point of the bistoury should not be directed laterally but straight back. The incision for a peritonsillar abscess is made through the soft palate above the tonsil. It is often necessary to plunge the instrument from one to two inches into the swelling before the abscess is reached. If care is taken to direct the point of the instrument straight back and not to the side, there need be no fear of causing injury by introducing the instrument too far. When the abscess is entered, pus will at once appear along the sides of the knife. On withdrawing the instrument the size of the opening should be increased by cutting parallel with the free border of the soft palate. In spite of a large opening, it sometimes becomes necessary after a few days to introduce a blunt probe and reopen the passage. A general anesthetic is contraindicated in these cases, and the local application of cocain is of little assistance. It is important, therefore, that the instrument used should have a fine point and a keen edge, and that the operation should be done as quickly as possible. The method sometimes recommended of making a small opening through the mucous membrane through which a blunt instrument is

plunged deep into the tissue, increases the suffering very greatly and has no advantage over the quicker and much less painful method of using a sharp instrument.

The treatment of tonsils which have been the seat of acute infection has become a much more important matter since the recognition of the frequency with which systemic infection occurs as the sequel of tonsillitis. Formerly, the situation was met by an attempt to remove part of the tonsil with a tonsillotome, provided the tonsils were large enough to be secured by this instrument. The operation was restricted almost exclusively to children. In adults the type of tonsil that could be operated on successfully by the method in vogue was rather the exception. Various methods were devised to treat such tonsils in adults. Fragments of the tonsils were removed with biting forceps, and the operation repeated several times, until a large part of the parenchyma of the tonsil had been removed. In other cases the surface of the tonsil was repeatedly cauterized with an electric point. In some cases the crypts were torn open with blunt or sharp instruments, followed by the introduction of an electric point into the enlarged pocket in an effort to obliterate the crypts.

In more recent years all these methods have given way to the operation of enucleation of the tonsils. The reason for the resort to a more radical operation has been twofold. In the first place was the failure in many cases to prevent recurrence of the attacks of acute tonsillitis by the older methods of operating as well as the better appreciation of the danger in subsequent attacks in cases where there has once been systemic infection such as arthritis, endocarditis or nephritis. In the second place it became apparent that in many cases where the tonsils had been partially removed or where the surface and crypts had been cauterized, even though there might be no subsequent attacks of tonsillitis, there often persisted a state of chronic infection of the tonsils which became a dangerous focus capable of causing systemic infection resulting in such serious conditions as chronic neuritis, cardiovascular degenerations, chronic arthritis and chronic nephritis. To prevent not only the possibility of a recurrence of acute tonsillitis, but also the possibility of persistent chronic latent foci of infection in the tonsil stubs, the enucleation of the tonsil has been resorted to.

A single attack of acute tonsillitis when not associated with systemic infection hardly warrants the advice to have the tonsils removed, unless this single attack results in unmistakable evidence of persisting infection in the tonsils. (*See Chronic Tonsillitis, following.*) Whenever, on the other hand, there develops a distinct tendency to recurring attacks of acute tonsillitis, or when a single attack of tonsillitis has resulted in such a serious systemic infection as acute endocarditis, nephritis or articular rheumatism, the advice should be given to have the tonsils removed, that is, enucleated.

CHRONIC TONSILLITIS

A great deal of progress has been made in recent years in the recognition of chronically infected faucial tonsils. The internist has called attention to the frequency with which chronic, often latent, foci of infection are responsible for the persistence of systemic infections resulting in chronic neuritis, chronic arthritis, cardiovascular degenerations and nephritis, as well as the probable etiological relation of these foci with such conditions as enlargement of the thyroid, gall-bladder infections, gastric and duodenal ulcers, and appendicitis. The result is that the specialist in diseases of the throat has been led to examine the tonsils much more closely than heretofore, and many cases of chronic infection of the tonsils are detected which were previously overlooked. Formerly, about the only type of chronically infected faucial tonsils which was recognized and given serious consideration was the type where the tonsils became chronically enlarged, especially when they showed a persistent state of congestion. The removal of such tonsils, particularly in children, has long been practiced, and it has long been recognized that the striking improvement in general health which so frequently follows this operation could be plausibly accounted for only on the assumption that the infected tonsils were producing a persistent though mild systemic infection.

In gathering the evidence which should place suspicion on the tonsils as a possible focus for infection, the history of recurring attacks of acute tonsillitis should have first consideration. Tonsils which are known to be the seat of such recurring attacks should always be suspected of harboring chronic foci of infection, exactly as we would condemn an appendix which is the seat of recurring attacks of acute inflammation. As pointed out in the previous section on acute tonsillitis, many cases of acute tonsillar disease pass unrecognized as such by the patient. The local symptoms are looked upon as the result of a sore throat but not of a tonsillar infection. The history of recurring sore throat even when the patient asserts that there have been no attacks of tonsillitis should always be regarded with suspicion. The history of an attack of quinsy or of a peritonsillar abscess is always suspicious since these conditions frequently leave persistent latent foci of infection in the depths of the tonsil.

An examination of the tonsil will disclose distinct evidence of chronic infection in a great many cases even when there is nothing in the history of the throat symptoms that would throw suspicion on these structures. Tonsils which are the seat of chronic infection are very often enlarged. The exposed surface of the tonsil as well as the neighboring tissue, especially over the anterior pillars, is often more or less congested. In many cases the crypts are enlarged and contain foul-smelling cheesy plugs.

Pressure with a blunt instrument along the outer boundary of the tonsil will often express large masses of epithelial débris from the deeper lacunae, and especially from the more embedded upper lobe of the tonsil. Occasionally by pressure in this way, pus can be expressed from a chronic abscess in the depths of the tonsil. The presence of cheesy deposits or even of pus is not restricted to the tonsils which are chronically enlarged but are as apt to be found in tonsils which through the hypertrophy of the connective tissue stroma have undergone a shrinking with elimination of a large part of the parenchyma. A particularly suspicious type is the tonsil which is deeply embedded between the layers of the soft palate, with only a small surface exposed to view even after the anterior pillar has been pulled aside. Tonsils of this type are often much enlarged and yet nothing is seen of them by the casual inspection of the pharynx. It is now a well recognized clinical fact that a tonsil which has been previously operated on and partially removed or where the surface has been scarred over by the use of the cautery, is especially likely to retain chronic foci of infection, capable of causing systemic disease. It is not uncommon when operating on tonsils to discover pockets of pus the presence of which was not disclosed by a careful previous examination.

These clinical facts, which have been observed over and over again by the men working on the tonsils, taken in connection with the rôle played by chronic foci of infection in the etiology of systemic disease, have brought about a decided change in our treatment of chronically infected tonsils. Local treatment of tonsils, the seat of chronic infection, has not been found to be of any very positive assistance in most cases. The complete enucleation of the tonsil is the one treatment which we have of making sure that the infection has been eliminated. This does not mean, however, the indiscriminate removal of tonsils even when there exists some of the evidence just discussed that the tonsils are not entirely normal. The decision to remove the tonsils depends on two factors. The first is, the character of the evidence of infection discovered in examining the tonsils. The second is, the presence as well as the character of a systemic infection, which the tonsils may be suspected of causing. Tonsils which are the seat of recurring attacks of inflammation should be removed. This applies as well to small as to large tonsils and as well to adults as to children. Tonsils which are decidedly enlarged, especially when the crypts contain foul-smelling, cheesy plugs or where the persistence of a distinct congestion indicates the persistence of infection, should be removed even though there is no evidence of acute attacks of tonsillitis. Tonsils from which pus can be expressed should be removed even though they are causing no local symptoms, and even though no evidence of systemic infection is recognized. A single attack of tonsillitis, even though the tonsils have not been left enlarged, if complicated by a serious systemic infection such as acute rheumatism, endocarditis or

nephritis, calls for enucleation of the tonsils as a prophylactic measure against the recurrence of the systemic trouble. Tonsils which are not the seat of recurring acute inflammation, which are not distinctly enlarged, and from which pus cannot be expressed but which do exhibit some of the evidence discussed above of chronic infection, such as the presence of cheesy deposits in the lacunæ, hardly call for removal unless the patient is suffering from a serious systemic infection, for which no other probable focus can be discovered. On the other hand, I have several times removed tonsils when the internist has advised the operation because the patient was suffering from a serious systemic infection for which no probable focus could be discovered, when there was no history of acute tonsillitis and where I had not been able to discover any local evidence of tonsillar infection, and I have been surprised at disclosing at the time of operation an abscess deep in the tonsil. The conclusion forced upon one by such experiences is that when a patient is suffering from a serious systemic infection which is known to be of focal origin, and when a thorough-going examination by a competent internist fails to discover any probable focus, one is justified in removing the tonsils, especially since it is known that they are the most frequent seat of such infection.

It is evident from this discussion of the treatment of chronically infected faucial tonsils that many cases can be handled intelligently only through the coöperation of the throat specialist and the internist. This is especially the case where systemic infection exists.

One encounters many cases, particularly in adults, where there is no suspicion of systemic infection and where the local findings in the tonsil hardly justify their removal, and yet where the lacunæ contain cheesy plugs, which cause more or less annoyance to the patient especially by giving an offensive odor to the breath. In such cases, one is often justified in attempting to relieve the trouble by repeatedly slitting open the offending lacunæ, by syringing out the cheesy plugs and by the use of the electric cautery. There are occasional cases, too, where both because of the presence of a systemic infection and from the local findings in the tonsils one would ordinarily be justified in removing these structures, but where because of a high blood pressure and a slow coagulation time the risk of a dangerous bleeding might deter one from the radical operation. In such cases one may try the safer though usually much less effective measures outlined above for getting rid of the tonsillar infection.

The enucleation of the faucial tonsils is not a minor surgical procedure, as was the older method of amputation of part of the tonsil. Enucleation, particularly in adults, where the tonsils have become adherent, as is frequently the case after a peritonsillar abscess, is an operation fully as difficult and because of the risk of subsequent hemorrhage fully as dangerous as an operation on the appendix. The failure to appreciate this fact has been responsible for not a few cases of fatal

hemorrhage, not to speak of permanent injuries to the throat when the operation has been undertaken by the practitioner inexperienced in the technic of this sort of work.

In children the operation can only be done under a general anesthesia. Ether is found to be the best agent for the work. Chloroform is contra-indicated, as it has been shown to be particularly dangerous in cases of marked hypertrophy of the lymphatic structures of the throat. Nitrous oxid, because of the increased bleeding and the necessity for haste in completing the operation, is not so suitable in the hands of most operators as is ether. In young children, moreover, it has been found to be decidedly more dangerous than ether. Such anesthetics as ethyl chlorid and ethyl bromid have been given up since they have been found to be practically as dangerous as chloroform. The handling of the anesthesia is more important than in most operations, since it is more difficult to give an anesthetic properly for a tonsillar operation. In the first place, unless the anesthesia is deep enough, the operator is working at a disadvantage because of the patient's gagging, and in the second place, an anesthesia pushed too far brings with it unusual dangers in operations on the tonsils, especially from the inhalation of the blood. For these reasons the advantage of having a trained anesthetist assist in tonsillar operations is becoming more and more recognized.

The position of the patient during operation is important. Some operate with the patient sitting upright, some with the head dropped back over the end of the table and others with the patient lying on the back. Some apply specially devised suction apparatus for keeping the field of operation free from blood, while others operate with the throat full of blood.

An operator may become accustomed to any of these methods of operation and does his work best when following the method to which he has become accustomed. All things considered, it is better for the patient to be in a reclining position while taking a general anesthetic. In the same way it is evident that, other things being equal, it is better for the throat to be free from blood during the anesthesia. The occurrence of abscesses in the lungs after tonsil operations performed under general anesthesia, is probably the result of inhalation of blood with infected material from the tonsils. We have found that having the patient lie on the side so that the blood will flow naturally from the mouth is the simplest way of overcoming the annoyance to the operator from the bleeding as well as the danger to the patient of inhaling the blood. The operator sits on a chair beside the patient and the lower tonsil is removed first. All bleeding should be checked before the patient is allowed to come out from the anesthesia.

The large number of different instruments that have been devised in recent years for this work speaks eloquently for the difficulties that have

been encountered by operators in undertaking the enucleation of the tonsil. No one method of operation is best suited for all cases. In children, the usual type of enlarged tonsil can as a rule be readily shelled out from its bed by forcing the tonsil by means of the finger through the opening of an old-fashioned Mackenzie tonsillotome. In other cases where the tonsils require removal but where they are not enlarged, and especially where they are of the embedded type, the operation is often accomplished with the least traumatism by seizing each tonsil with the forceps, and drawing it toward the median line. The upper pole is then loosened by cutting with a sharp scalpel the mucous membrane along the line of its attachment to the tonsil. With this accomplished, the tonsil can be pulled through the loop of a stiff wire snare, and cut off slowly enough to prevent bleeding.

The operation for enucleation of the tonsils in adults is quite a different procedure, since in most cases it is best to do the operation without employing a general anesthetic. With the use of a local anesthetic the risk to the patient is distinctly less than when ether is used. The bleeding is less, and is more readily controlled with the patient conscious and in the upright position. On the whole the discomfort to the patient with a properly administered local anesthetic is very much less than when ether is employed. Nitrous oxid as an anesthetic is not especially suitable to these cases, first because with the usual type of tonsils in adults where they are not greatly enlarged, the patient experiences no pain, provided the operator has had sufficient experience in the technique of local anesthesia. In the second place, the cases where the local anesthesia fails to give complete insensibility to pain, are the cases where the tonsils are greatly enlarged, and especially where they are adherent through inflammatory reaction. In these types of cases the time required to do properly the necessary dissection is not sufficient when gas anesthesia is used.

In nervous individuals it is often a decided advantage to administer hypodermically morphin $\frac{1}{6}$ to $\frac{1}{4}$ gr. with atropin before the patient is taken up to the operating room. The operation should not be undertaken soon after a meal, as the annoyance from gagging is thereby greatly increased. Local anesthesia is begun by applying with a cotton swab around the attachment of the tonsil 5 per cent. cocain made up in an adrenalin solution. When the patient begins to experience the local effect of the cocain by the development of a sensation of fullness in the throat, a solution of novocain, $\frac{1}{2}$ of one per cent., should be injected about the tonsil with a suitable curved needle. A few drops are injected beneath the mucous membrane at one or two points along the posterior pillar. As much as $\frac{1}{2}$ dram of the novocain may be injected into the lower pole of the tonsil. The most important part of the local anesthetic is the injection of a sufficiently large quantity of the novocain into the base of

the tonsil. The proper point for making the injection can usually be determined by locating the outline of the tonsil through the soft palate. The needle is then pushed through the anterior surface of the soft palate deep into the tissue. If the point of the needle has failed to penetrate under the tonsil the injecting fluid will escape through the lacunæ. In cases where the embedded velar lobe of the tonsil is very large or where, as the result of peritonsillar inflammation, the normal demarcation between the base of the tonsil and the neighboring tissue has been obliterated, it may be quite difficult to get the solution injected so that it does not escape through the tonsil lacunæ.

With the local anesthesia completed the patient is directed to hold the tongue depressor in place while the operator seizes the left tonsil with a suitable forceps held in his left hand. The tonsil is drawn downward and toward the median line. With a straight sharp scalpel held in the right hand, the operator incises the attachment of the mucous membrane along the anterior upper part of the tonsil. Then without detaching the forceps this instrument is seized quickly with the right hand and with the scalpel in the left hand the mucous membrane is incised along its attachment just in front of the posterior pillar. In the same way, the right tonsil is dissected from its attachment, especially around the upper part. Only after both tonsils are dissected free in this way is the effort made to pull the first tonsil through the loop of the stiff wire snare. By tightening the snare slowly, the tonsil can be removed as a rule with very little bleeding.

The control of subsequent bleeding may often be much more difficult than the operation itself. In case the primary bleeding does not stop promptly and completely, the bleeding point must be searched for at once, and seized with a curved artery forceps. The usual point of bleeding is from the tonsillar artery near the middle of the tonsil fossa. Occasionally the bleeding point is in the upper part of the tonsil fossa or near the lower pole. The artery forceps may be left in place for 15 to 20 minutes after the patient has been taken from the operating room. Very troublesome is the bleeding which trickles down the esophagus without the patient knowing it. The nausea associated with the accumulation of blood in the stomach increases greatly the anxiety of the patient. When a secondary bleeding occurs in a nervous patient it is usually an advantage to administer morphin hypodermically $\frac{1}{6}$ to $\frac{1}{4}$ gr. with atropin. This alone frequently results in a prompt cessation of the bleeding. The simplest mechanical means of stopping the bleeding is by pressing a ball of cotton soaked in peroxid into the tonsil fossa. The excess of peroxid should be squeezed out of the cotton and the pressure kept up as long as the patient will permit. In case this does not suffice to stop the bleeding, it is usually advisable to proceed at once to search for the bleeding point. This is done by first wiping out all the clots from the fossa, then with

reflected light the bleeding point is looked for and when found, seized with the curved artery forceps.

The patient is better off sitting up in bed with a back rest for a few hours after the operation, and is often made more comfortable by having ice bags around the throat. A simple gargle every three or four hours begun the day after the operation and kept up for about a week is the only after treatment that is called for. A teaspoonful of bicarbonate of soda in a tumblerful of warm water is as useful as any gargle. The unpleasant taste in the mouth, which persists for several days after the operation, may be relieved somewhat by the occasional use of a gargle of peroxid diluted in water.

ACUTE NASAL SINUITIS

Acute inflammation of the mucous membrane lining the nasal accessory sinuses is a common complication of acute nasal catarrh. In some of the grip epidemics involvement of the nasal accessory sinuses is extremely common. The inflammatory process may be restricted to the sinuses on one side, affecting one or several simultaneously, or it may involve all the sinuses on both sides, producing a condition of pan-sinuitis. An acute abscess about the root of an upper molar or even a bicuspid tooth not infrequently ruptures into the antrum and produces an acute maxillary sinuitis. Acute sinuitis is always associated with more or less marked subjective symptoms, which vary from a sensation of fullness or stuffiness on the affected side to that of pressure or even severe pain over the region of the sinus involved, that is, over the frontal or maxillary sinuses or between the eyes. The recognition of an acute sinus inflammation presents no great difficulty. The process can usually be suspected from the subjective symptoms complained of. In addition to the sensations over the region of the involved sinus and the blocking of the nasal passage on the affected side, there is usually present a marked increase in the nasal discharge. The transillumination test will usually give a positive finding for both the maxillary and frontal sinuses, easily recognized when the process is unilateral (*see* discussion of transillumination tests under chronic sinuitis). The skiagraph will assist in making the diagnosis, especially in cases of frontal sinus trouble. Should the skiagraph leave any doubt concerning the maxillary sinus, this can readily be cleared up by irrigation of the sinus, by introducing a cannula into the natural opening, or by puncturing the nasal wall with a suitable instrument either in the middle or the inferior meatus.

The treatment of acute sinuitis is chiefly directed to the relief of the subjective sensations. If the maxillary sinus has become infected by a tooth abscess, it is important first of all to have this abscess taken care

of by a dentist. The symptoms of nasal obstruction are relieved by reducing the turgescence of the nasal mucous membrane. The simplest means for relieving this condition is by nasal irrigation, using a hot normal salt solution. In order to avoid the risk of carrying the infection up the Eustachian tube into the tympanum, it is best to direct the patient to draw the salt water up into the nose. This can be facilitated often by the use of a straight glass tube with a suitable bulb on the nasal end. A great deal of relief is usually afforded by spraying the nose with the following preparation: menthol gr. 8, camphor gr. 4, oil of eucalyptus m. 3, albolin oz. 2. The patient should be directed to draw the albolin spray back through the nose. A weak solution of adrenalin, 1:10,000, sprayed into the nose is often an effective way of relieving the intranasal swelling. The most effective method for relieving the intranasal obstruction is by applying with a cotton swab a $\frac{1}{2}$ per cent. solution of cocain in 1:10,000 adrenalin along the under surface of the middle turbinated body. The subjective sensations of pressure and of pain result from the retention of secretion in those sinuses which have their openings under the middle turbinated body. This includes the maxillary and frontal sinuses, as well as the anterior ethmoid cells. The relief afforded by applications along the free edge of the middle turbinated body lasts usually for several hours and in some cases for the larger part of the day. Suction by means of a suitable apparatus may be employed to withdraw secretion from the accessory cavities in cases of acute sinusitis. The value of this method of treatment is secondary to that outlined above. The use of the electric light head bath devised by Brünings is usually an effective method of relieving intranasal turgescence and the subjective symptoms dependent on this condition. Severer cases should be kept in bed. Aspirin, 5 gr., repeated every 3 or 4 hours, often affords relief. In other cases, an opiate may be necessary.

The necessity for treatment further than that just outlined for the relief of acute sinusitis arises only in the exceptional case. One occasionally encounters a case where, because of the failure to secure proper drainage through the normal openings by the methods already given, the pain occasioned by the retention of secretions becomes so severe that resort must be had to surgical measures. In the case of the maxillary sinus the cavity can be irrigated by puncturing the nasal wall of the sinus either in the middle or the inferior meatus. A few irrigations usually suffice to clear up the process. Should the severe symptoms persist, a large opening can be quickly made through the nasal fontanelle in the middle meatus. For the relief of retention in the frontal sinus and in the anterior ethmoid cells a resection of the anterior end of the middle turbinated body will usually suffice. In exceptional cases this may have to be followed by an exenteration of the anterior ethmoid cells. Irrigation of the frontal sinus by the introduction of a suitable cannula will relieve the

pain occasioned by the retention in this sinus. There are very few cases where all efforts to secure intranasal drainage for an acute frontal sinusitis fail. In these cases one may be forced to open the sinus by an external operation in order to relieve persistent severe pain.

CHRONIC NASAL SINUITIS

Chronic inflammation of the nasal accessory sinuses appears under several distinct forms. The trouble may be limited to one sinus or there may be involvement of all the sinuses even on both sides of the nose. Chronic foci of infection in the nasal sinuses may assume an important part in the etiology of systemic infection. The close relation of the sinuses to the orbit permits of a direct extension involving the eye, a condition which is particularly apt to occur from disease of the ethmoid. The anatomical relation which frequently exists between the optic nerve and the posterior ethmoid cells and sphenoid sinus permits of an involvement of this nerve by an extension of the infection from these sinuses. The profuse discharge of pus in some cases of chronic sinusitis draining back into the pharynx may cause digestive disturbances. The detection, therefore, of cases of chronic sinusitis and the institution of the proper method for relieving this condition becomes a very important question.

The symptoms complained of by the patient are not so characteristic as in cases of acute sinusitis. The persistence of a profuse purulent discharge from the nose should always arouse suspicion of a chronic accessory sinus disease. A unilateral discharge is particularly characteristic of sinus empyema. In a good many cases, the process is more or less latent and the trouble can be detected only after a careful search. In cases where the amount of discharge is slight it will sometimes form in crusts about the nasal orifice of the affected sinus. Headache is characteristic of chronic sinusitis, especially during periods when there is some obstruction to the escape of the secretion from the sinus, or during the period of an acute exacerbation of the chronic process.

The method of procedure by which the detection of chronic sinusitis is made, consists in the first place of an intranasal examination by means of reflected light. Purulent secretion found in the nose should arouse suspicion of chronic sinusitis. The reappearance of pus in the course of a few minutes after the nasal passages have been carefully cleansed, is proof that the secretion comes from some reservoir where it has been previously accumulating, that is, from an accessory sinus. If the pus reappears under the middle turbinated body, that is, in the middle meatus, it means an involvement of the maxillary sinus or frontal sinus or of the anterior ethmoid cells, or of all three. If the pus reappears between the middle turbinated body and the septum, it can come only from the

sphenoid sinus or the posterior ethmoid cells. In a great many cases of chronic sinusitis, the amount of secretion is so slight, especially during the latent stages, that little or no secretion is found in the nose, and none reappears in a reasonable period after cleansing. The second step in the examination is to apply the transillumination test. Should this show a distinct shadow over one maxillary sinus while the other remains clear, it should arouse strong suspicion that the sinus is involved, and in case the shadow is on the side where pus was found to reappear in the middle meatus, there is little room to doubt the presence of maxillary sinusitis. Not infrequently when the bones are heavy, transillumination leaves one in doubt, because of the presence of a shadow over both sinuses. When, on the other hand, transillumination shows the absence of a shadow on either side, we are fairly safe in concluding that there is no maxillary sinus trouble. The transillumination of the frontal sinus is not as a rule conclusive because of the frequent occurrence of small sinuses which fail to give a positive difference on the two sides even when only one sinus is affected. In many cases, especially where the sinuses are not small, the transillumination will be found so clear as to preclude the possibility of frontal sinus disease. In other cases, too, when the sinuses are not small, the presence of a distinct shadow over one sinus when contrasted with the clear illumination of the opposite side, leaves little room to doubt the presence of a frontal sinus empyema, especially when this finding is combined with the reappearance of pus in the middle meatus.

In the cases where the intranasal examination and the transillumination tests do not exclude the possibility of sinus disease, a skiagraph should be made. This will be of value in determining not only the presence of trouble, particularly in the case of the frontal sinus, but the skiagraph will also show the exact size of the frontal sinus. The final step in making a positive diagnosis in suspected cases is by irrigation of the sinus in question. This method has its greatest use in cases of maxillary sinus infection. The irrigation is accomplished by catheterizing the normal opening in the middle meatus or by puncturing the nasal wall of the sinus in the middle or the inferior meatus. If pus is washed from this sinus and reappears again in the middle meatus it must come from either the frontal sinus or anterior ethmoid, or from both. Irrigation of the frontal sinus is not so simple and cannot always be accomplished, even after the anterior end of the middle turbinated body has been removed. If pus reappears in the middle meatus after irrigation of both maxillary and frontal sinuses, it can come only from the anterior ethmoid cells. Irrigation of the sphenoid sinus is more readily carried out.

This preliminary discussion of the detection of chronic sinusitis will help to clarify the problems one encounters in relieving these conditions. Not infrequently a tooth abscess has been the starting point for a chronic

maxillary sinusitis, which in turn has infected the other sinuses on that side. It is important in such cases that the offending tooth be properly taken care of first of all. The primary factor in the successful treatment of most cases of chronic sinus disease is to secure adequate drainage and ventilation of the sinus. This accomplished, the condition often tends to heal without further treatment. In the case of the maxillary sinus, this drainage can be accomplished by making a sufficiently large opening either in the middle meatus in the region of the nasal fontanelle, where the most fragile part of the nasal wall of the sinus is found, or under the inferior turbinated body. A large permanent opening made in this way is usually sufficient to bring about a cure of chronic maxillary sinusitis. The operation may be followed by daily irrigation with a warm normal salt solution through the opening into the sinus. This the patient can be taught to carry out by himself for a few weeks until the pathological secretion has disappeared. In intractable cases a more radical operation may be called for. This consists of making an incision under the upper lip and lifting the periosteum over the anterior wall of the sinus. This wall is then removed and a greatly thickened mucous membrane in the sinus everted away. The operation is completed by making a large permanent opening into the inferior meatus of the nose.

The cure of chronic frontal sinusitis is undertaken in the same way by securing adequate drainage into the nose. Since the frontal sinus disease is usually complicated by a more or less extensive involvement of the anterior ethmoid cells, the first step in securing drainage for the frontal sinus is the removal of the anterior part of the concha media, followed by a partial or a complete exenteration of the ethmoid cells, depending on the extent to which they appear to be involved. Finally an effort is made to increase the size of the nasofrontal opening. Considering the relation of the ethmoid cells to the orbit and to the cribriform plate it is evident that operations in this region should be undertaken only by those who have made a most careful study of the regional anatomy of this part, and are also perfectly familiar with the technic of intranasal operations. This operation for securing better drainage from the frontal sinus may be followed by regular daily irrigation of the sinus with a warm normal salt solution. This too as a rule the patient can acquire the ability to carry out at home. Many cases of chronic frontal sinusitis go on to a perfect recovery after this treatment has been carried out. In other cases the trouble persists because of permanent alterations in the membrane lining the sinus, usually in the form of polypoid degenerations, which are sometimes found completely filling the cavity of the sinus. The disfigurement, more or less marked, which is certain to result from the scar of an external operation on the frontal sinus is a contraindication to this procedure except in unusual cases where after every effort has been made to secure relief by drainage through the intra-

nasal route, the severe pain continues or symptoms of an intracranial extension appear.

The radical treatment of chronic empyema of the ethmoid labyrinth or of the sphenoid sinus is much simpler. This consists in the exenteration of the ethmoid cells and the resection of the anterior wall of the sphenoid sinuses. Both of these operations are now feasible and are carried out intranasally by the specialist skilled in the technic of this sort of work. Sometimes it is not feasible to accomplish the complete exenteration of the ethmoid labyrinth at one sitting, and in these cases repeated sittings require a great deal of perseverance both on the part of the patient and of the surgeon to search out and drain all infected cells. Even a small concealed packet of pus in such cases may constitute the focus for the persistence of a most serious systemic infection.

The results obtained in the treatment of chronic nasal sinuitis may be summed up as follows. By securing adequate drainage by intranasal operations most cases can be permanently cured. The sinus most likely to persist in discharging pus in spite of this treatment is the frontal sinus, and here the advisability of an external operation is particularly contraindicated because of the conspicuous scar which must result. In those cases where by intranasal surgery we fail to bring about a definite cure of frontal sinuitis, this treatment affords in most instances relief from the chief symptoms complained of, namely, frontal pain, occasioned by the obstruction to the outflow of pus from the sinus. The complete elimination of foci of infection from remote ethmoid cells presents great difficulties and these may be met with when an external operation is undertaken as often as when one relies upon intranasal surgery. The complete eradication of chronic foci of infection, therefore, in cases where these are suspected of causing systemic disease may not always be entirely feasible, especially where such foci are located in remote ethmoid cells or in the frontal sinus.

Hyperplastic Ethmoiditis.—In connection with chronic accessory sinus disease mention should be made of the condition of polypoid degeneration of the mucous membrane lining the ethmoid cells, as well as of the membrane about the nasal orifice of these cells, especially of that covering the uncinate process in the middle meatus. This form of ethmoiditis is not primarily a suppurative disease. It is not uncommon, however, for a subsequent infection of the ethmoid, such as frequently occurs from an attack of influenza, to produce a suppurative condition which, because of the impaired drainage occasioned by the presence of polypi, is very prone to become chronic. This condition of polypoid degeneration of the ethmoid seems often to be predisposed by the presence of an anatomical variation whereby the normal ventilation and drainage of the ethmoid cells are readily impaired. A large percentage of the cases occur in patients where the concha media is wedged so tightly between the septum and the outer

nasal wall as to practically close the middle meatus, into which the chief ethmoid cells open. The anatomical relation is such that but a slight congestion of the mucosa of the nose is required to close tightly the openings of the cells. The symptoms observed in these cases, particularly in the early stages, are chiefly attacks of sneezing associated with a profuse watery nasal discharge. There may be at times a sensation of fullness or pressure between the eyes. The voice often lacks its normal resonance, just as occurs frequently in acute coryza. Sooner or later in a great many of the cases distinct symptoms of asthma develop. Indeed, it is rather the exceptional case of asthma where distinct evidence of a hyperplastic ethmoiditis cannot be detected. A casual examination of the nose very often fails to discover this condition, for the reason that an inspection of the middle meatus is interfered with because of the anatomical condition described above and by the time the polypi begin to make their appearance from under the concha media the change in the ethmoid cells is already of long standing. In such cases, where because of the symptoms one is led to suspect a hyperplastic ethmoiditis, it is necessary, by means of a long bladed nasal speculum (a Killian speculum), to pry open the middle meatus in order to detect evidence of beginning polypoid degeneration. The condition is, of course, a chronic one and there is no tendency for a spontaneous recovery. In the early stages the improved ventilation of the ethmoid cells, accomplished by the resection of the anterior half of the concha media, seems often to be sufficient to bring about a cure. In the later stages only the complete exenteration of the ethmoid labyrinth by a radical intra-nasal operation will be of permanent value. These operations bring relief more frequently to the strictly nasal symptoms than they do to the associated asthma. Failure to cure the asthma in some cases may depend upon our inability to accomplish such a complete exenteration of the ethmoid cells as to prevent the recurrence of polypi.

CHAPTER IV

DISEASES OF THE ESOPHAGUS

BERTRAM W. SIPPY

49. Line 37 *read*:

method of dilating esophageal strictures, the writer **would certainly** urge the use of this

51. Line 12 *add* after "advised.":

By means of the silk, the wire guide is introduced until its bulbous point has reached the pylorus.

52. Line 21 *add* after "gastrostomy.":

An extra set of smaller bulbs, a finer wire guide and a spiral introducer made correspondingly smaller in diameter are required for the enlargement of strictures too tight to admit the No. 10 (French scale) bulbous point on the end of the wire guide.

Line 28 *add* after "opening.":

Adopting the same method of procedure, the writer has successfully dilated narrow strictures located in the upper portion of the stomach.

55. Lines 31-32 *read*:

Deglutition becomes unusually difficult and painful. The passage of **the dilating bulbs causes** unusual pain. Both pain and obstruction may be greatly

Line 36 *read*:

If, notwithstanding the use of dilating **bulbs**, appropriate diet, and

56. Line 35 *read*:

and treated **over 100 cases since 1903.**

58. Line 25 *add* after "esophagus.":

Röntgen ray examination shows retention of barium solution in the esophagus. The lower portion of the elongated shadow gradually tapers to a point below the diaphragm. Irregularities commonly seen in the barium shadows when the obstruction is caused by carcinoma or cicatricial narrowing at the cardiac orifice of the stomach are absent.

Line 26 *read:*

The onset of symptoms may be sudden or gradual. In most cases the first symptom

64. Lines 37-38 *read:*

sure necrosis and periesophageal abscess formation. Thrush may invade **the mouth, pharynx and esophagus** at the same time. In adults the growth of

65. Lines 24-32 *read:*

lowed esophageal **bulbs** should be passed as early as a week or ten days afterward. The patient should take a few swallows of olive oil just previous to the passage of the **bulbs**. In severe cases the narrowing may already be so great that only small-sized **bulbs** may be used. In a few days larger sizes should be used, gradually dilating every three or four days, until the maximum sized esophageal **bulb** has been passed. This should be accomplished before extensive cicatricial narrowing has had time to develop. If the tissue destruction has been great it is often necessary to pass **dilating bulbs, once each week for a few weeks; subsequently the intervals may be lengthened according to the requirements of the individual case.**

CHAPTER V

DISEASES OF THE STOMACH

JACOB KAUFMANN

108. Line 13 *add* after "ulcer.":

[In considering the etiology of acute and chronic peptic ulcer of the stomach and duodenum due consideration must be given to the results of the experimental work of Rosenow. (Rosenow, E. C., and Sanford, A. H., "The Bacteriology of Ulcer of the Stomach and Duodenum in Man." *Jour. Inf. Dis.*, 1915, XVII, 219.) Our clinical experience working with Rosenow shows that streptococci gain entrance to the blood stream from confined infection about the jaws, sinuses of the head and tonsils and may cause infection of the submucous tissues of the stomach and duodenum. The microorganisms cause thrombosis or embolism of the arteries of the submucosa and consequent hemorrhage into the tissues. The submucous tissues are thus deprived of nutrition, more or less devitalized and the overlying tissue is readily digested by the gastric juice. Acute ulcer occurs and if the microorganisms remain in the tissues healing is prevented and chronic ulcer results. There seems to be no question that ulcer of the stomach and duodenum may occur in the manner described.

There are other causes which diminish the blood supply in local areas of the submucosa of the stomach and duodenum and the overlying tissues may be digested and ulcer result. Infection as a cause of ulcer of the stomach and duodenum is important because it helps to explain the incidence of ulcer, and it also probably explains the difficulty of the cure of ulcer. Uninfected wounds of the stomach heal readily. It is fair to assume that wounds which do not heal are either infected or the blood supply to the tissues at the base of the ulcer is deficient.

—EDITORS.]

113. Line 14 *add* after "vessel.":

[Emetin hydrochlorid, gr. 1 hypodermatically, has a marked hemostatic effect in pulmonary and gastric hemorrhage. The mode of action is not

known. The dose may be repeated every 3 to 6 hours for a day. If used too long toxic neuritis may result.—EDITOR B.]

139. Line 43 *add* after "treatment.":

[In the treatment of chronic ulcer of the stomach, one must first bear in mind the fact that both acute and chronic ulcer may be caused by hematogenous infection. The source of hematogenous infection is frequently found in alveolar abscesses, infected tonsils and sinusitis. The removal of the focal source is indicated as a primary step to prevent continued bacteriemia and renewed infection of the submucosa of the stomach and duodenum. The infectious microorganisms in the tissues of the wall of the stomach and duodenum will probably disappear in time and especially if the general resistance of the patient is improved by proper hygienic measures. I doubt very much if the use of autogenous vaccines would be of benefit.

In the medical management of chronic ulcer of the stomach and duodenum the method elaborated by Sippy (Sippy, B. W., "Gastric and Duodenal Ulcer, Medical Cure by an Efficient Removal of Gastric Juice Corrosion," *Jour. Am. M. Ass.*, Chicago, 1915, LXIV, 1623) is a rational and practical one. Dr. Sippy believes that the corrosive action of the gastric juice is due to the presence of free HCl. Combined HCl has no corrosive action. Consequently he gives the patient a form of management which will as nearly as possible rid the gastric juice of free HCl. This is done with alkaline powders and at the same time a bland diet with frequent feedings is given. The result of the management is ascertained and the medication is increased or decreased by the use of the stomach tube and examination of the aspirated contents of the stomach at definite periods during the day. The patient is preferably treated in a hospital; is kept in a recumbent posture. The patient is first fed with a small quantity of equal parts of good cream and milk, one-half ounce each, given every hour beginning at seven o'clock in the morning and continued until seven o'clock at night. The amount of milk and cream is gradually increased day by day until the patient may take three ounces of each or six ounces altogether every hour, thirteen times per day.

The alkaline treatment consists of two sets of powders; one of ten grains each of bicarbonate of soda and of the heavy oxid of magnesia, and the other of ten grains each bicarbonate of soda and subcarbonate of bismuth. The soda-magnesia powder is given at six-thirty in the morning, half an hour before the first feeding and is repeated every two hours until eight-thirty at night. The soda-bismuth powder is given at seven-thirty in the morning and repeated every two hours until seven-thirty at night. The stomach is aspirated with proper technic at six-thirty or at nine-thirty A. M., at four-thirty and at nine-thirty P. M., and the test is made for free HCl. If it persists an additional quantity of bicarbonate of soda is given with each powder until such a time as the gastric juice shows no free HCl. When there is great irritability of the stomach, a level teaspoonful dose of subcarbonate of bismuth may be given in the fasting stomach of the morning and after the last aspiration at nine-thirty P. M. In the event that there is gastrosuccorhea the stomach may be aspirated at midnight and also early in the morning. When the gastric contents contain no free HCl during the day a well cooked cereal is given once, then twice, then three times a day at the hourly feedings and with it is taken the six ounces of milk and cream. Soft boiled eggs are added in the same way to other hourly feedings until the patient is upon a bland diet of cream, milk, well cooked cereal and soft eggs, giving him a sufficient amount of nutritious food to keep him well nourished. Later the patient may have purées of vegetables, baked, mashed and creamed potatoes, creamy soups without a meat stock and later stewed fowl, lamb, veal, boiled and baked fish and other easily digested bland foods. Practically

all patients learn how to use the stomach tube without discomfort, and when the patient leaves the hospital he continues to pass the stomach tube at least once a day, preferably at nine-thirty at night, and he makes the simple test for the presence of free HCl in the gastric contents. He may add or diminish the amount of the alkalies taken, dependent upon the presence of free HCl in the gastric contents. The heavy oxid of magnesia in one of the powders is laxative in its effect. More or less of these may be taken, dependent upon the condition of the bowels. Under this management Dr. Sippy and his associates have treated a great number of patients with chronic ulcer of the stomach with apparent excellent results.—
EDITORS.]

CHAPTER VI

DISEASES OF THE INTESTINES

HENRY WALD BETTMANN

213. Line 27 *read:*

terference is **indicated but not always necessary**. The experience and

Line 30 *read:*

ation is **far** preferable to medical treatment. Watchful medical treatment

243. Line 3 to **244.** Line 3 (inclusive) *substitute:*

It is customary to divide cases of visceroptosis into two groups, the congenital and the acquired. The term congenital is in one sense a misnomer. The ptosis, itself, is not inherited but merely the tendency thereto. Neither the stomach, the intestines nor the kidney prolapses before the age of puberty. According to R. H. Smith, at the age of puberty there is a widening of the pelvis and a compensatory narrowing of the waist. In weak, relaxed and badly nourished children, these changes are pronounced and the ptoses are apt to occur along with other changes. There are many reasons why the term congenital visceroptosis should be given up altogether and why the so-called cases of congenital visceroptosis should not be classified as cases of visceroptosis at all. For nearly seventy years it has been well known that congenital prolapse of the abdominal organs is only a part, and not always an important part, of a condition of general constitutional asthenia. In 1899 Stiller designated this condition as "*asthenia universalis congenita*," and the same year H. Strauss described it as a *coördinated expression of the constitutional inferiority, "Minderwertigkeit," of various organs*. The term "*habitus asthenicus*," or constitutional asthenia, has since then become prevalent.

The essential truthfulness of Stiller's presentation as applied to a certain large group of cases is generally accepted. Stiller laid especial stress on the long narrow flat thorax, the small bones, the slight panniculus adiposus, the mobile tenth rib and what he called a vulnerable nervous system. His general conclusion has met with practically universal acceptance, viz.: that the symptoms in this type of visceroptosis are not due so

much to the visceral displacement as to the vitiated muscular and nervous system of the individual.

Intensive study of the "habitus asthenicus" has disclosed other constituent elements. Among the congenital defects of development (Williams, *Bost. M. & S. J.*, June 17, 1915) are failure of the colon to rotate completely into the right flank; failure of complete fusion between the right mesocolon and the posterior parietal peritoneum, resulting in cæcum mobile (Wilms); failure of the layers of the great omentum to fuse. Goldthwaite (*Bost. M. & S. J.*, June 17, 1915) lays emphasis on the smallness of the spine, and the deformity of the lumbar vertebrae. He also accepts as quite characteristic for this type an abnormal shortness of the large and small intestines. He calls attention to the undersized heart, the small lungs, the slender feet with their unnaturally high arches. Other writers have noted that in this type the female genitalia are often poorly developed.

To the study of structure has been added the study of function. It has been found that in children of this build orthostatic albuminuria is not uncommon; weak digestion and constipation are prevalent; and Uhlman has recently demonstrated that the liver in these subjects is physiologically inferior, as determined by the ready appearance of galactosuria after the administration of 30.0 g. galactose (*Arch. f. Verd.*, Nov., 1915).

As many of these patients show a lessened reaction to pilocarpin, i.e., a certain grade of sympatheticotonia, it is possible that lessened hepatic function indicates a vitiated nervous system.

When we sum up these observations we find that we have gathered into one group certain individuals of a particular body-form or habitus who are apt to present some or many of the following characteristics:—a vulnerable nervous system of neurasthenic type; a weak muscular system; certain skeletal defects; physiologically weak hearts, kidneys, livers and digestive organs; displacement of one or more abdominal viscera. Chiefly through custom we still refer to these patients as being "cases of visceroptosis," although the malposition of abdominal viscera is only one item out of many. It is in fact not always present, frequently does not play an important part in the symptomatology and may easily become a misleading factor in the treatment if an undue amount of attention is paid to it. The error is commonly made of ascribing offhand any existing digestive disorders to the ptosis as such—especially to assuming that the constipation is the obvious result of the prolapse (although we know that prolapse of and by itself does not produce constipation), and to direct all our therapeutic efforts to changing the position of the viscera by bandages, rest cures and finally by operative procedures.

244. Line 4 read:

R. H. Smith (21, 22) has reached **interesting** conclusions.

245. Line 43 *read*:

tion is **frequent**, and the stools appear as small, hard lumps. Espe-

246. Line 29 *read*:

can be taken by the more careful management of **convalescence** from wasting

254. Line 11 *add* after "overlooked.":

[In recent years the number of recognized cases of trichiniasis has greatly increased. Studies of the pulmonary symptoms sometimes observed in trichiniasis, the finding of trichinae in the blood and spinal fluid, have stimulated interest in the disease and led to a more general knowledge of its symptomatology. Rural epidemics which are usually confined to a small number of persons, arising from eating imperfectly cooked meat from a pig killed on the farm and distributed to the neighbors, have been noted, and are probably not infrequent.—EDITORS.]

CHAPTER VII

DISEASES OF THE LIVER

HENRY WALD BETTMANN

258. Line 4 *read*:

gence in beer, spirits, **sweet** or greasy foods; it may follow any excessive meal,

264. Line 35 *read*:

appear in the large majority of cases. **Salvarsan is the remedy of choice.** The treatment must be prolonged

273. Lines 14-15 *read*:

are advised by many clinicians **and** in my opinion are **often useful in preventing recurrent attacks.** Tyson (23) says: "I

Line 20 *read*:

had attacks without my knowledge." **Personally, I doubt the efficacy of the remedy.**

276. Lines 21-22 *read*:

a white blood count in this emergency because **some** cases of purulent cholecystitis are not accompanied by **marked** leukocytosis. If it is possible to

277. Line 43 *read*:

Fick (11) has shown that, whereas autopsy records show a larger and

278. Lines 28-31 *read*:

cer usually does not occur in cases which give a typical gallstone history. The etiological relation between cancer and stones has not been absolutely proved. As Neus-

Lines 42-43 *read*:

in whom symptoms recur after even a successful operation. Recent statistics show a return of symptoms in from one-third to one-fourth of the cases after cholecystotomy. J. J. Buchanan (Trans. Am. Surg. Ass., Vol. 33, p. 316, 1915) estimates that after cholecystotomy only 70 per cent. of the patients remain well. Graff and Weinert (Beitr. z. klin,

Chirurgie, Vol. 92, p. 339, 1914) studied the end results in 124 cholecystectomized patients. Only 73 per cent. were cured.

281. Line 17 *read*:
given with advantage. Fifteen or twenty drops well diluted and taken before or

292. Line 9 *read*:
11. Fick. Erfolg d. Karlsbader Kur und Chir. Behand. d. Gallen-

CHAPTER IX

DISEASES OF THE PERITONEUM

J. T. HALSEY

311. Line 20 *add* as footnote to "satisfactorily"¹:

¹ A combination of antipyrin, gm. 0.3 to 0.5 (gr. v-vii), with chloral, gm. 1.0 to 1.3 (gr. xv-xx), given orally or rectally, is often a very satisfactory substitute for morphin in these cases.

312. Lines 16-18 *read*:

Bowels.—In the past there has been much diversity of opinion among physicians and surgeons as to the use of cathartics, **but today all authorities agree** with Ochsner in his strong condemnation of catharsis in any

313. Line 18 *add* as footnote to "et al."³:

³ Crile reports 391 cases of acute peritonitis with only two deaths.

317. Line 2 *add* as footnote to "enema."¹:

¹ Crile has recently offered an explanation of the manner in which opium or morphin may be beneficial in these conditions. According to his views the mechanism of septic shock is similar to, if not identical with, that of surgical shock. He believes that in both of these conditions these drugs prevent damage to important nerve centers, especially those presiding over the circulation.

Line 19. *Add* as footnote to "nourishment."²:

² For several years past the author has advocated the addition to these enemata of sodium bicarbonate ($\frac{1}{2}$ to 2 per cent.) and believes that he has seen good results therefrom. It is usually well borne by the patient.

Line 40 *read*:

Boas has shown the real danger of severe or fatal poisoning which may

Line 44 *add* after "failed.":

For several years past, surgeons have been employing pituitary extract as a means of moving the bowels in these cases. It is given hypodermically 1 c.c. (m. xv) at a time, and may be repeated at half hour intervals.

318. Line 35 *add* after "regarded.":

All experimental evidence with which the author is familiar fails to support the view that strychnin can be of value here, and some of it indicates that the only

effects to be expected from it will be harmful rather than helpful. Personally I am against its employment.

321. Line 5 *add* as footnote to "X-rays¹":

¹Recently Kümmel has strongly advocated their employment in conjunction with surgical measures. He claims 50 per cent. of cures, but his cases are not very numerous nor had sufficient time elapsed for us to accept his views.

Line 23 *add* as footnote to "(Graser)²":

²The author questions the correctness of this view and has not hesitated to tap very large and distressing effusions in a limited number of cases and has seen no apparent harm but apparently good results from so doing.

323. *Add* under "References":

Crile. Surg. Gyn. & Obst., Apr., 1915, p. 415.

Kümmel. Centralbl. f. Chir., 1913, p. 468.

II. DISEASES OF THE RESPIRATORY TRACT

CHAPTER I

DISEASES OF THE NOSE

BURT R. SHURLY

330. Line 34 *read*:

If the atrophic process is attended by thyroid deficiency, **thyroid proteid extract or** iodin (gr.

337. Line 16 *add* after "origin.":

Remarkable results have been claimed by Horn of San Francisco from the use of a vaccine prepared from the isolated infecting microörganism which he claims is the etiologic factor.

CHAPTER II

DISEASES OF THE LARYNX

BURT R. SHURLY

338. Lines 16-17 *read:*

The early use of calomel in 1/10-grain doses until ten **or fifteen** are taken **is advised**. This should be followed by the usual saline in the

Line 22 *read:*

A room saturated with moist **soda** steam is grateful and comforting. A

339. Lines 14-15 *read:*

often give great relief. **The cough in adults may be relieved with heroin gr. 1/12-1/24.**

340. Line 10 *read:*

as argyrol, **20-40** per cent., or alummol, 20 per cent. Spasms of the glottis

Line 41 *read:*

able instrument **as the Mackenzie** that will hold firmly the proper-sized cotton

341. Line 4 *add* after "benefit.":

Laryngitis resulting from recurrent infection should have proper surgical treatment for adenoids, tonsils or accessory sinuses according to the foci of infection present.

343. Line 30 *read:*

solution as a down spray can be used to the larynx and **proves** grateful.

347. Line 14 *read:*

remedy. It should be prepared daily from a 40 per cent. solution **and the initial strength should be 3 per cent. in glycerin.** Until

CHAPTER III
DISEASES OF THE BRONCHI

ROBERT D. RUDOLF

350. Line 10 *read*:

Is it a primary infection of the respiratory mucosa; **is it a local manifestation of some general infection such as measles or typhoid fever;** or is the catarrh

Line 26 *read*:

done in this chapter, the **practitioner must** always use his discretion as to how

351. Line 6 *add* after "account.":

It was noticed early in the present war that Canadian troops remained well while under canvas during very bad winter weather on Salisbury Plain, but very many suffered from bronchial catarrh as soon as they were housed in huts.

356. Line 30 *read*:

stupe, **which is a hot fomentation with a teaspoonful of turpentine sprinkled over it.** The stupes should be renewed every four hours, and after the

360. Line 1 *read*:

torants are **unreliable**, but I should not like to be without

Line 18 *add* after "uncertain.":

The action of aconite, however, is very slight and the writer (*Amer. Jour. Med. Sci.*, Dec., 1912) found that even much larger doses than pharmacopial ones failed to affect the pulse rate or blood pressure.

361. Line 15 *read*:

cated as it disturbs the alimentary functions less than does opium or morphin. It goes well with ipecacuanha wine and spirit of chloroform,

362. Lines 7-9 *read*:

but its effects must be closely watched, **when it is decided to use it.** It

is perhaps best to give a small dose, which may be repeated once or twice during the night at the discretion of the attendant. **The drug is rapidly excreted and thus will not accumulate in the system.** The B. P. syrup contains 10 grains of the drug in

364. Line 9 *add* after "employed." :

It has been experimentally shown by D. V. Cow (*Lancet*, May 29, 1915) that oxygen is much more effectual for the relief of gas poisoning (chlorin) when atropin has been first given. This drug apparently first dilates the bronchials and then allows the chest to empty and fill more completely.

Line 38 *add* after "trial." :

In France where the method has been much used lately. Martinet's oxygenator is usually employed.

366. Line 4 *read* :

He will probably require some tonic, most commonly cod liver oil or iron, **or the two combined.**

Line 30 *add* after "Egypt." :

When a patient has "gone South" for the winter it is most important that he does not return to his northern home too soon in the spring. One often sees this error committed with the direct results.

368. Line 32 *read* :

constant menace to these people **from the dust thus raised.**

369. Line 5 *add* after "possible." :

They are also especially susceptible to tuberculous infection and must hence avoid this as far as possible.

371. Line 16 *read* :

taining a **very oxidizable** fat in a very fine state of division, and those preparations of it

373. Line 13 *add* after "morning." :

(The writer has frequently found this mixture of great value.)

378. Line 43 *read* :

little longer sometimes, and may be repeated at intervals of a few **weeks**

379. Line 11 *add* after "necessary." :

The tendency to asthma depends upon two factors: (a) the irritability of the bronchial neuromuscular apparatus, (b) the amount of reflex irritation from the respiratory tract or elsewhere. If the irritability be sufficiently great the attacks may occur from very little reflex irritation or may even appear to occur spontaneously. If the irritation be great, then it may produce spasm in the bronchial muscles not very irritable.

382. Line 28 *add* after "same." :

Nerve-racking surroundings, such as occur in the present great war, tend to bring fits in those so predisposed, but have no tendency in my experience to precipitate paroxysm of asthma.

383. Line 10 *add* after "effects.":

Further, it appears to relax the lungs as these are more permeable to the X-rays than usual and the diaphragm is lower in people taking the drug.

385. Line 2 *add* after "experience.":

Diphtheritic antitoxin has been much used lately in warding off attacks and seems in some obscure way to do so. Thus J. A. Reuter (*N. W. Medicine*, March, 1908) so *treated* 60 cases including *himself* and relief seemed often to be permanent. The dose used was 2,000 units, which might be repeated. But it has often been noted that when the administration of antitoxin has been followed by alarming symptoms, the patients happen to have been asthmatics. Thus out of 23 such cases recorded by H. F. Gillette (*Jour. of Amer. Med. Ass.*, Feb. 13, 1909) 16 had suffered from respiratory trouble.

386. Line 15 *add* after "attack.":

Pyridin.—Pyridin is a valuable inhalant here. Ten to 15 drops inhaled from a handkerchief may give rapid relief.

387. Line 20 *read*:

prisoned by the spasm of the circular fibers **and at the same time relaxes the circular muscular fibers.**

388. Line 27 *add* after "nation.":

Atropin.—Atropin hypodermically administered is of great value in the paroxysms; 1/100-1/70 grain so given will often cut short an attack. Recently it has been shown experimentally by D. V. Cow (*Lancet*, May 29, 1915) that when given to animals it fully dilates the bronchials.

391. Line 6 *read*:

are in true asthma (q.v.). **The adrenalin is best used locally, either as a 1:2000 spray or 1:1000 ointment.**

394. Line 44 *add* after "risk.":

In one case in which the patient had a hectic fever, profuse sweating, marked emaciation, with about 300 c.c. daily of most foul sputum, the writer gave great relief by nitrogen compression of the lung. The temperature became normal, the sputum almost ceased and the patient gained 7 pounds a week.

399. Line 13 *add* after "doses.":

Care should be taken not to give a further injection while any reaction is present. There are now many tuberculins each having its advocates.

Line 26 *read*:

given by the mouth **and S. Solis-Cohen confirms this (N. Y. Med. Jour., 1912)**

400. Reference 12 *read*:

12. **Cushny, A. R.** Pharmacology and Therapeutics, 282.

CHAPTER V

DISEASES OF THE PLEURA

JOSEPH A. CAPPS

476. Line 41 *read*:

Before using the aspirating cannula on the patient test its **patency**

482. Lines 20-21 *read*:

of the fluid with that of the blood they hoped to favor absorption, **but had little success.**

Line 26 *add* after "safety.":

The author finds it expedient to allow air to be sucked in through the cannula at intervals during the process of evacuation, if much force is necessary to draw out the effusion. The danger of air infection is no greater than when the abdomen is opened in tuberculous peritonitis.

490. Line 22 *add* after "type.":

In these cases the effusion is often under very little pressure and must be pumped out. As the lung may be adherent and may not expand a strong negative pressure is created in the chest which favors congestion and rapid refilling. Such an undesired result may be obviated by allowing air to be sucked in through the cannula until no more will enter. Air should, however, not be forced in.

493. Line 24 *add* after "hypodermatically.":

ARTIFICIAL PNEUMOTHORAX FOR THERAPEUTIC PURPOSES

In the majority of pleural effusions evacuation of the fluid is followed by expansion of the lung and obliteration of the space previously occupied by the fluid. But in many old serous effusions and in most chronic hemorrhagic effusions of tubercular or cancerous origin, the lung is so bound down by adhesions that it fails to expand, thereby leaving an empty space under high negative pressure. As a consequence the exudate quickly collects and the inflammation is often aggravated.

In recent years we have made a practice of admitting ordinary air by

spontaneous suction at intervals during the operation and at the termination allowing as much air to enter as will. This method substitutes an air cushion in place of fluid against the lung. Since air is absorbed with comparative rapidity the lung is given a chance to expand gradually, while the reformation of fluid is discouraged. In hospital practice, where repeated observations of the chest can be made with X-ray, one can plainly see the advantages of artificial pneumothorax in these cases.

III. DISEASES OF THE CIRCULATORY SYSTEM

CHAPTER I

DISEASES OF THE PERICARDIUM

ALEXANDER MCPHEDRAN AND WILLIAM FLETCHER MCPHEDRAN

519. Line 6 *add* after "avail.":

[In pericarditis occurring in rheumatism, sodium cacodylate in doses of 3 to 5 grains given daily by deep hypodermic injections has been used. This is discussed under the Complications of Acute Arthritis.—EDITORS.]

525. Line 38 *read*:

nizable paracentesis alone will probably be efficacious. **Solution of adrenalín (1:1000), 1 c.c., may be injected after paracentesis in the hope of arresting the exudate.** In the patient's

527. Line 16 *read*:

parcel of a general septicemia the outlook is naturally very bad. **A vaccine prepared from the exudate may prove useful after drainage.**

528. Line 36 *add* after "irregular.":

Brauer showed two cases at the meeting of the International Medical Congress at Budapest in 1909. In one the result was excellent; in the other only moderate relief resulted because the heart muscle was much injured by the inflammation.

CHAPTER II

DISEASES OF THE CIRCULATION, EXCEPT PERICARDITIS

CHARLES SPENCER WILLIAMSON

548. Line 24 *read*:

We may, for convenience sake, distinguish **two** groups of cases:

Line 31 *add* after "continued.":

One of the most remarkable facts about the heart is its unwillingness to undergo dilatation even after very decided muscular efforts. This applies not only to the normal but to the pathological heart as well. Using the very accurate teleröntgen method, which is free from the subjectivity, as well as certain inaccuracies of the orthodiagraphic procedure, the writer has recently shown that the hearts of practically all normal individuals and about one-half of the ambulatory heart cases, some in broken compensation, respond to exercise within their powers, by a definite diminution in size. This is important in applying gymnastics remedially.

557. Line 28 to **558.** Line 2 (inclusive) *substitute*:

Auscultatory Method.—This method, which has recently come into wide use, has the very great advantage that by it the diastolic pressure can be obtained with far greater accuracy than by the methods just described. The same apparatus is used in either method. By means of a stethoscope applied to the brachial artery just distal to the cuff, the normal tapping sound of the artery is noted. The pulse is then obliterated by the inflation of the cuff, and the air allowed to escape until the first tapping sound reappears. This point marks the systolic pressure. The tapping sound grows louder as the column of mercury drops, and remains loud until the point of minimal pressure is reached. It then suddenly changes to a feeble, impure sound. The height of the mercury column at which this occurs is regarded as the diastolic pressure. At a point varying from five to ten mm. lower, the sound disappears entirely. The advantages of this method are its greater accuracy, particularly in reference to the measurement of the diastolic pressure. Its chief disadvantage is that it is difficult, in fat arms, to hear the change in the sounds clearly.

Of the various forms of apparatus in use in America, the Erlanger has proven itself in the writer's hands the most satisfactory from the standpoint of accuracy.

558. Lines 33-34 *read*:

better than a very rough approximation to the true value. **For accuracy, one should use either the auscultatory method or the Erlanger apparatus.**

565. Lines 16-17 *read*:

2. Permanently irregular heart (**auricular fibrillation**).

3. Paroxysmal tachycardia.

570. Lines 14-42 *substitute*:

AURICULAR FIBRILLATION.—This is the newer term for the very common type of arrhythmia hitherto called *pulsus irregularis perpetuus*. It occurs in chronic endocarditis associated with the various valve lesions and in the various chronic degenerations of the myocardium. In this type of pulse there is a total lack of the normal rhythm. Indeed it often happens that many of the waves are so small that they fail to reach the periphery, so that the pulse rate, as taken at the radial, may be markedly slower than when taken by auscultation. Inasmuch as the existence of this type of pulse probably invariably has for its basis an organic lesion, it is of far greater import, clinically, than the extrasystole. Once established, it is not probable that this arrhythmia ever entirely disappears. On the other hand the extrasystole often disappears instantly and permanently.

The characteristics of this pulse are due to the fact that there exists in the auricles the condition known as fibrillation, a virtual paralysis of the auricles, in which the auricular walls are maintained in a position of diastole, and a true systole does not take place. The term fibrillation has reference to the fine fibrillary twitchings, which can be seen on its surface, in experimental animals. The exact cause is still obscure, but it has been suggested that there is "functional fragmentation" of the tissues giving rise to a large number of independent impulses. In cases where the pulse is irregular and over 120 per minute, auricular fibrillation is generally present. When decompensation is attended by a rapid irregular apex beat, this is almost invariably due to fibrillation. It is perhaps the most readily recognizable of the arrhythmias, and is by far the most important, since it is, above all others, most amenable to treatment. The existence of this type of arrhythmia, with a rapid pulse, marking beginning cardiac failure, is the classical indication for the exhibition of digitalis.

580. Line 32 *read*:

value **in the management of myocardial insufficiency.**

581. Lines 5-7 *read*:

the least reliable. **This applies chiefly to the condition of badly broken compensation. In auricular fibrillation, with very slight disturbance of compensation, the pulse is, of course, the most reliable guide to digitalis medication.**

590. Lines 4-31 *substitute*:

Nevertheless, it is just under these very conditions that the drug is badly borne, in that it increases nausea and vomiting if these be present, or produces them if they were previously not in evidence. Just here is where the physician is apt to make the mistake of discontinuing the drug. The remedy is to give it intramuscularly or intravenously in adequate doses, and these symptoms disappear with the improvement in the circulation. The writer has many times made the observation that in cases where digitalis by mouth has produced no results, the same drug intravenously promptly induced a restoration of compensation. It is probable that, under these conditions, absorption from the intestines is greatly interfered with.

ARRHYTHMIAS.—It is probably true to say that no *type of arrhythmia, in and of itself, ever furnishes an indication for digitalis.* Neither tachycardia, simple or paroxysmal, extrasystoles, nor the various forms of cardiac neurasthenia are improved by digitalis. Even auricular fibrillation, in and of itself, is not an indication for its exhibition. It is only when the pulse becomes rapid (over 100 at rest), i.e., because of beginning cardiac weakness, that digitalis is indicated. It should be stopped when the pulse reaches sixty or when coupled beats develop. In the rare condition of auricular flutter digitalis seems to be of service in many cases. Its action in these cases is not thoroughly understood. Heart block, of itself, calls for no treatment, and in this condition the use of digitalis may, by its action in depressing conductivity, increase the block, *yet if the heart, because of impaired compensation, requires digitalis, it should be given quite irrespective of the existing block.* In other words, the indication for the use of digitalis lies in the impaired compensation with its concomitant symptoms, and not in the mere presence of the heart block, however marked this may be.

595. Line 40 to 596. Line 2 (inclusive) *substitute*:

Physiologically Standardized Galenical Preparations.—Titrated preparations (leaves and tinctures) have been on the German market for some years, and, in general, are reliably standardized. In this country standardized preparations are now available, although many so-called "Standardized Preparations" are very far from being either accurate or reliable. Edmunds and Hale have shown that some of these may vary within very wide limits in their physiological activity, and are correspondingly untrustworthy.

598. Lines 24-26 *read*:

intravenous injection. **Since the introduction of digipuratum in ampule form, the writer has had opportunity of subjecting the ampules to critical clinical tests, and has found them highly satisfactory. Hypodermically, the dose is approximately the same.**

599. Lines 6-16 *substitute*:

Intramuscular injection is usually preferable to the hypodermic administration, as it is less painful and the drug is more rapidly absorbed. This is especially true when there is a considerable degree of edema.

In the most severe cases, the efficient procedure is to give the drug intravenously, using precisely the same technic as is described for strophanthin. Two ampules (16 frog units) may be given at one time in emergencies. In general, the dosage is a little less than when the drug is administered orally. After a little practice with the technic of the injection they are so readily administered that the writer during the past few years has used them with ever increasing frequency. As compensation improves oral administration may be resumed.

600. Lines 33-36 *read*:

tack of decompensation, of such severity as to threaten life. **Recent experience has shown that the above doses are unnecessarily large, and at times dangerous. One-half milligram is now regarded as a full dose.**

671. Line 40 *add* after "measured.":

Inasmuch as the body manufactures hemoglobin but very slowly, the administration of iron in some suitable form is indicated after free venesection, until the hemoglobin is again approximately normal.

697. Lines 33-36 *read*:

plete emptying of the heart. **The writer has shown (loc. cit.) that not only does the normal heart respond to exercise within its powers by a diminution in size, but that many damaged hearts of all kinds respond in the same manner.**

708. Lines 10-33 *substitute*:

Cardiac Insufficiency from Syphilis of the Myocardium.—The researches of the past few years have all tended to show that syphilis affects the myocardium as well as the aorta in a much larger percentage of cases than has hitherto been supposed. While it has always been recognized that syphilis plays a rôle in the development of arteriosclerosis and hence indirectly is a factor in the production of myocardial degeneration from coronary sclerosis, it seems that we must go further, and recognize many cases as due directly to the spirochetes. They have been found in the heart muscle in large numbers. Clinically the recognition of such cases is difficult. The Wassermann reaction is perhaps the best guide, but in all cases where syphilis can reasonably be supposed to be the prime causa-

tive factor, antisyphilitic treatment should be instituted. Probably the purest cases of this nature which come under the observation of the physician are those of myocardial insufficiency which sometimes develop in the course of a severe secondary syphilis. Several such cases have come under the writer's care and in these the results of treatment can be really said to be brilliant. Under conditions as they actually exist the physician will be called upon to institute prophylactic treatment for the cardiac insufficiency of syphilis chiefly in the sense that when treating cases of syphilis he will be alive to the possibility of any cardiac weakness being due to that disease, and will take the appropriate steps in treatment, which should be kept up for a longer period of time than usual.

719. Lines 32-34 *read*:

application of an elastic bandage about the arm. **In most instances, the dose of strophanthin need not exceed one-half milligram, and with this dose accidents due to overdosage are practically excluded.**

720. Line 9 *read*:

may be continued hypodermically, **or better, intramuscularly.**

729. Line 31 to **730.** Line 11 (inclusive) *substitute*:

Cardiac Insufficiency from Syphilis of the Myocardium.—The number of cases in which the spirochaeta pallida is the principal or exclusive cause of myocardial disease has been shown by recent investigations to be much larger than commonly assumed. The organisms have been found in the heart muscle by Warthin in a surprising percentage of cases examined, and it can scarcely be questioned that they are the causative factor in the pathological changes found, even though actual gummata are not present. The Wassermann reaction has made it possible to achieve something nearer a rational diagnosis of this condition than was previously possible. Of course, in any case it is difficult to determine clinically what rôle may be played by the other factors which we know tend to produce the various forms of myocardial insufficiency.

The results which one may look for depend of course, above all, upon the age of the syphilis and the damage which has already been inflicted upon the heart muscle by the spirochetes. Unfortunately the Wassermann reaction throws no light on either of these points, hence it is well not to expect too much from antisyphilitic treatment except when the syphilitic infection is a recent one, and the myocardial insufficiency is not great. The writer's experience is that the best results are obtained by a vigorous course of inunctions, with iodids in moderate doses. The salvarsan of Ehrlich is, according to the best opinion, not well suited for such cases. If used at all, it should be administered in minute doses. With outspoken insufficiency, rest in bed, digitalis, etc., are indicated, as in non-syphilitic cases.

734. Lines 23-35 *substitute*:

Removal of Foci of Infection.—The quite astonishing frequency with which endocarditis is kept active by the existence of some focus of infection, makes it the paramount duty of the clinician to search for such foci and when found to take measures for their removal. The more frequent of these are found in diseased tonsils, alveolar abscesses, adenoids, and suppurative processes in the accessory sinuses. The teeth especially should be examined by a competent röntgenologist, as apical abscesses are often found entirely unsuspected by the patient and even by the dentist. Other less frequent sources are the gall bladder, prostate, appendix, fallopian tubes, and the tissues around the nails. Because of the danger of recurrent endocarditis, every intercurrent disease, and especially tonsillitis, polyarthrititis, and chorea, should lead to careful and repeated examinations of the heart.

739. Lines 20-44 *read*:

and the supposed cirrhosis disappeared in a fortnight's time. It should never be lost sight of that nausea and vomiting that indicate the full physiological effect of digitalis has been overstepped. This vomiting, as Eggleston and Hatcher have shown, is central in origin, hence will occur even if the drug had been given hypodermically or intravenously. Using standardized preparations, such vomiting is rare. This is, of course, quite a different matter from the vomiting which occurs when such a nauseating preparation as the infusion is given to a patient with venous congestion of the gastrointestinal tract. In such a case the remedy is plain—the dose of the drug should be reduced or it may be omitted altogether for twenty-four hours.

740. Lines 1-25 *substitute*:

Auricular Fibrillation.—This condition, the *pulsus irregularis perpetuus* of former writers, demands especial attention, inasmuch as it is by far the most important and frequent abnormality of the heart beat met with in every day hospital practice, especially among patients with outspoken cardiac weakness. Its significance lies in the fact that it invariably marks the existence of an organic lesion—a degenerative or inflammatory process in the myocardium, either alone or in conjunction with some valvular lesion, generally of the mitral orifice.

Therapeutically, there is no other cardiac condition in which one can accomplish more than in this, and yet it must be noted that the underlying condition is usually a permanent one. Fibrillation is constantly seen in the badly compensated mitral lesions, and the brilliant results in such cases from digitalis are due to the effect of that drug on the fibrillation. It must be borne in mind that it is not the fibrillation per se that is the indication for digitalis, but rather the fact that when fibrillation occurs with a rapid heart (over 100 per minute in the recumbent posture) it

indicates cardiac weakness. It often happens that this occurs when the other signs of cardiac weakness are difficult to make out, hence the value of recognizing this rhythm. The arrhythmia per se tends to produce slowing of the circulation, and overfilling, particularly of the auricles. Now by increasing the force of the contraction and by impeding the conductivity, digitalis tends to break up this vicious circle, and restore normal conditions. The drug should not be pushed beyond the point where the heart rate reaches sixty. Coupled heart beats indicate impending danger under these conditions. In all respects the treatment is that outlined in chronic myocardial insufficiency.

Auricular Flutter.—This rare condition has only recently been recognized. It is closely related to paroxysmal tachycardia, and is associated nearly always with a heart block. Except with special methods, it is difficult of recognition. It, too, is associated with cardiac weakness but the relationship is not clearly understood. Digitalis is the only drug which has proven effectual and it has not been always successful. In general, the treatment must be of the underlying condition, if this can be determined.

Extrasystoles (*Premature Contractions*).—The clinical significance of these is still an open question. Undoubtedly many of them are dependent on nervous causes and others on temporary toxic causes. They may occur in individuals who consider themselves normal, and be accidentally discovered. After being present, off and on, for weeks and months, they sometimes disappear permanently. Per se they require no especial treatment except when the premature beat produces disagreeable subjective sensations, i.e., cardiac neurasthenia.

Pulsus Alternans.—This is invariably the sign of a damaged heart, and calls for the treatment applicable to chronic myocardial insufficiency.

744. Lines 4-9 *substitute*:

Inasmuch as the majority of cases of endocarditis are associated with rheumatism, most of the matter of prophylaxis centers about the prevention of this disease. To this end, the body should be carefully searched for possible foci of infection, and every effort should be made to extirpate these thoroughly. It is remarkable how insignificant a focus can give rise to a severe endocarditis.

Lines 15-18 *read*:

the present time be accurately estimated, **but it is** absolutely proven that the spirochaeta pallida can produce valvular lesions. **This is almost always an insufficiency of the aortic valves, and is produced by an extension of a syphilitic aortitis to the cusps.**

745. Lines 22-23 *read*:

be directed toward minimizing the damage. The strictest rest **in bed, to be of real service, must be maintained for some three or four months.**

746. Lines 37-39 *read*:

conclusions being drawn, it seems at the present writing to be the method from which there is most to be hoped in the future. (See article on **Vaccine Therapy**.) [We have seen no permanent good results from the use of vaccines in ulcerative endocarditis.—Editors.] The ingestion of large quantities of fluid, and especially sub-

762. Line 31 to 763. Line 17 (inclusive) *substitute*:

SYPHILITIC AORTITIS

The importance of syphilitic aortitis as a distinct clinical entity has been strongly emphasized in the last few years. The pathological picture is quite distinctive, and the presence of the spirochete leaves no doubt as to its specific nature. The condition is essentially a chronic mesaortitis, with small-celled infiltration, and especially about the vasa vasorum. Calcification, so common in the arteriosclerosis of old people, is nearly always absent.

From the clinical standpoint the salient points to be noticed are the frequency with which the condition occurs under forty-five, its tendency to attack the ascending arch, involving the coronaries with the early production of angina pectoris in many instances, and the association of other syphilitic conditions, such as tabes. Aortic insufficiency is common and in the absence of definite evidences of endocarditis, should arouse the suspicion of syphilis. A positive Wassermann reaction is obtainable in most instances. Since X-ray examinations have become so universal, the beginnings of aneurysm in this locality are seen quite frequently.

The importance of recognizing syphilitic aortitis is very great, especially in the cases associated with aortic insufficiency which sometimes occurs within two or three years after the syphilitic infection. In just these cases very decided improvement under antisyphilitic treatment can be brought about.

Treatment.—Given a fairly definite diagnosis, especially with a positive Wassermann reaction, treatment should be promptly instituted, and should be vigorous and thorough. Bearing in mind the great danger of the development of angina pectoris and aneurysm, if indeed their beginnings be not already present, it would seem rational to treat the condition as if it were a newly acquired lues, thus erring, if at all, on the side of safety.

770. Lines 12-15 *read*:

of the greater liability to disturbances of conduction in this affection. **The frequency of syphilitic aortitis, as a cause of angina pectoris, is now well recognized. Improvement, under thorough antisyphilitic treatment, is often marked, especially in fairly recent infections.**

772. Lines 22-25 *substitute*:

Heart block of the milder grades demands no treatment. In cases where it is associated with myocardial insufficiency, digitalis may and should be given precisely as if no heart block were present, despite the theoretical tendency of this drug to increase the block.

788. *Add* under "References":

DIGITALIS

Eggleston, C., and Hatcher, R. A. The Emetic Action of the Digitalis Bodies. Jour. Am. Med. Ass., 1913.

CHRONIC MYOCARDIAL INSUFFICIENCY

Williamson, Charles Spencer. The Effects of Exercise on the Normal and Pathological Heart. Amer. Jour. Med. Sci., April, 1915.

ARTERIOSCLEROSIS AND ARTERITIS

Warthin, Aldred Scott. Heart Lesions Produced by the Spirochæte Pallida. Amer. Jour. Med. Sci., May, 1914.

GENERAL PHYSIOLOGY OF THE MYOCARDIUM

Lewis, Thomas. Clinical Disorders of the Heart Beat. 2nd Edition, 1913.

IV. DISEASES OF THE BLOOD

CHAPTER I

THE ANEMIAS

C. F. MARTIN

810. Line 6 *read*:

saline solution is advisable **or transfusion is performed.** (See Pernicious Anemia.)

Lines 20-26 *substitute*:

Arsenic and iron in combination have been recently insisted on by C. Aubertin. He points out that their respective actions differ in anemias. While arsenic induces new formation of red cells, the iron brings about hemoglobin formation and fixes it to the cells. Where then a combination of numerical and qualitative loss has occurred, the combined treatment is curative. As a rule it is well to employ the two, not simultaneously, but in succession, beginning with the one most required according to blood findings.

Musser recommends a combination of iron and arsenic with sodium glycerophosphate, which he prefers to the citrates of iron for hypodermic use as being painless. Fourteen cases were treated by him in this way, the injections being given intramuscularly, in some instances weekly, in some daily. Only one of the patients failed to respond promptly. (See also page 820 on hypodermic use of iron.)

Line 31 *add* after "here.":

Bickel recommends the use of thorium-X, especially in obscure secondary anemias of doubtful origin, and considers it the best remedy available for giving the initial impetus to an increased hemopoiesis.

He cites a case of a girl aged 19 in whom the red corpuscles numbered 1,700,000 and the hemoglobin was 45 per cent. Fifty thousand Maché units were given intravenously, followed by 30,000 to 50,000 by mouth daily. The red corpuscles rose under this treatment in six weeks to 5,200,000, and the hemoglobin to 88 per cent. (For further details on treatment by radioactivity *see* under Pernicious Anemia.)

812. Line 36 *add* after "months":

Summary.—Severe cases require rest in bed, in open air, a diet rich in albuminous content, and easily assimilated. The alimentary canal requires special attention with a view to attaining as nearly as possible intestinal sepsis and regularity of evacuations. For this reason naphthol and cascara are recommended as a preliminary to the use of any hematinics. Iron in Bland's pill is enough. Small doses will suffice and should be readministered over a long enough time (several months) in order to obtain permanent results. Often it is wise to repeat a course of iron every few months.

813. Line 34 *add* after "needs.":

Maillart's observations are of interest, inasmuch as he attributes the healthiness of Genevese to the preponderance of vegetables in the diet and to the special Genevese stew of green vegetables. Essential anemias, he states, are rarely seen about Geneva.

816. Line 33 *add* after "accumulated.":

This view is supported by several recent contributions. Hoffmann and Muller found experimentally that the bone marrow of animals fed upon iron after having been artificially rendered anemic, was much redder and richer in erythroblasts than that of the control animals. Schmincke made a careful comparative estimation of the total erythrocyte mass, number of red corpuscles, and hemoglobin content, before, during, and after iron administration. He found, in the twelve cases investigated, an increase in the total mass of erythrocytes and in the number of red corpuscles, while the hemoglobin rose more slowly, especially at first. This he regarded as conclusive evidence of the theory that iron, by stimulating the essential elements in the bone marrow, leads first to increased hemopoiesis and only secondarily, and much later, to a rise in hemoglobin of the individual corpuscle.

824. Line 26 *add* after "vomiting.":

It is essentially a hemolytic anemia, the cause being probably indirect. As a rule urobilinuria and stercobilin excess occur, and a slight icterus. The spleen is usually enlarged due to one of two causes: either hyperfunction (hemolysis) or excess introduction of red cells. The hemolysis is further expressed by the varying degrees of hemosiderosis. It must be remembered that every pernicious anemia may go over into the aplastic form (absence of regenerative power).

825. Line 7 *add* after "prognosis.":

Remissions have been lengthened and life perhaps prolonged, but reports of permanent cures are as yet doubtful.

Line 22 *read*:

Summary of Treatment Recommended.—It has been our habit in the Royal Victoria Hospital to place those

Line 25 *add* after "remarkable.":

Our patients are placed at rest in bed and at once a thorough search for possible sources of infection is instituted. This includes first of all the

teeth (X-ray pictures), the gums for pyorrhea, the sinuses, the alimentary canal, and the genito-urinary tract. Then having attended to all sources of infection we incline to early and copious transfusion where possible, and after several such treatments we prefer splenectomy and again further transfusions of blood (*see infra*). Ac. mur. dil. by mouth is further given to aid digestion and prevent diarrhea.

826. Line 24 *add* after "believe.":

Radium, Thorium-X, Actinium-X.—The peculiar properties possessed by metals of the radium group, of undergoing more or less rapid atomic disintegration with discharge of chemical energy, while emitting emanations consisting of rays of varying quality and penetrative power (alpha, gamma, and beta rays), lend to these substances a powerful biological action which is capable of direct therapeutic application. The discovery of radioactivity was followed by a wealth of literature and experimental work. As a result radium with its allies has been proved to have a definite effect upon the physiological processes of hemopoiesis, blood coagulation, blood pressure, uric acid and general metabolism, and ferment activity. Conclusive clinical evidence is still wanting, however, as to its specific value in individual diseases.

In larger doses radium is an endothelial and general cellular poison. In smaller doses its effect upon the blood picture is *to produce a rise in the erythrocytes, which may amount later to a polycythemia*, and an early rise in the leukocytes with a later leukopenia.

Recently *thorium-X* and *actinium-X*, derivatives of the radioactive metals of the same name, have been employed instead of radium in internal medicine.

Thorium was first thought of as a possible therapeutic agent in 1898, when the radioactivity of its salts was discovered by Mme. Curie. In 1902 Prof. Rutherford demonstrated that emanations similar to those of radium were given off by it and that these would render radioactive the walls of the container. Its remarkable effect in stimulating the formation of red blood corpuscles was next noted. These facts led Prof. Bickel (1912) to try the action of thorium-X in pernicious anemia. His present method is to give 50,000 Maché units once every four days intravenously until three doses are given, followed by 20,000 Maché units daily by the mouth, the whole quantity divided into three parts, one of which is taken after each meal. The results were surprisingly good, only one case out of a number treated being unsuccessful. A typical case was that of a man, almost moribund, with red cells 960,000, Hb. 50 per cent; 50,000 Maché units were given daily by the mouth for over ten months. In six weeks the blood picture became normal, erythrocytes, 4,610,000, Hb. 90 per cent., poikilocytosis gone. Six months later, in spite of persistent Repeated improvements and relapses followed in spite of steady adminis- thorium treatment, a relapse occurred, the red cells falling to 2,080,000.

tration of thorium-X and cholesterin daily. The effects of thorium-X in pernicious anemia were thus seen to be transitory, but it was of value in restoring the patient to temporary health when other measures had failed. Bickel recommends it especially in the secondary anemias, where he believes thorium-X in small doses persisted in over a long period to be the best remedy known for giving the initial impetus to increased red cell formation.

Thorium-X has also been recommended by Arneth. In one case where arsenic had failed, repeated small doses of thorium-X (intravenously injected) produced a marked remission. Gradual increase in red cells and leukocytes followed, with a differential white count approaching the normal. Large doses are condemned. No claim is made by him for a cure of pernicious anemia by means of thorium-X.

Actinium-X has a remarkable degree of radioactivity, producing the shortest lived emanations of all the radium elements. It sinks in 30 seconds to half its original volume, while radium emanations take a month and thorium 10 minutes to fall one per cent. The therapeutic effect of this powerful substance has been made the subject of an elaborate study by Lazarus. After proving its relative harmlessness on himself and on animals experimentally, he proceeded to the treatment of various diseases, including one severe case of advanced *pernicious anemia*. The patient, a woman of 51, had a blood count of 1,300,000, Hb. 32 per cent., marked poikilocytosis with many normoblasts and a relative lymphocytosis. Arsenic, both subcutaneously and internally, had been tried without effect. Small doses, 20-30 electrostatic units (20,000 to 30,000 Maché units), were given daily, divided into three parts, one part taken after each meal, with good effect, the red cells rising to 2,500,000, and the hemoglobin to 50 per cent.

The easy application of the form of radioactivity supplied by actinium and thorium-X places it within the reach of the ordinary practitioner. In daily doses of 20-30 electrostatic units, divided into three parts and given after each meal, the treatment continued for two to four weeks. It may be tried in all cases where irradiation is indicated, both as a supplementary measure and also especially where arsenic has failed, or is contraindicated. Lazarus suggests combining the short-lived elements actinium and thorium-X with radium, thus obtaining together the intensity of action of the former and the lasting radioactive effects of the latter. (For therapeutics of radium see Chap. II, following, on Leukemia.)

Line 33 *add* after "ceases.":

Croftan reports brilliant results in several cases, and concludes that this treatment when supported by the ordinary hygienic measures, good feeding, etc., yields excellent results in about half the cases in which it is employed. Hess followed Croftan's procedure in five severe cases, with marked success in three. Frequently in our own experience, HCl alone has been followed by prolonged remissions, with return of the blood picture and general condition to a temporary normal state.

829. Lines 24-41 *substitute*:

Salvarsan ("606").—Salvarsan is one of the most efficacious agents in the treatment of pernicious anemia, but like all other methods of treatment it is not curative—though it sometimes produces marked lengthening of remissions and rapid amelioration of symptoms. The dose is .3 to .6 gm. intramuscularly at intervals of days or weeks. B. Bramwell used it with success some years ago and more recently has favorably compared its use in 21 cases with that of Fowler's solution in former cases. There was no history of syphilis in the cases. Five of the cases were quite well, some four years after treatment; thirteen died from the disease. Hobhouse, Boggs, Leede, Maynard, and many others have recorded results with varying success.

Salvarsan rather than neosalvarsan is preferable. The drug is best given intramuscularly in order to obtain a more continued effect, and the dose at first should be .3 gm. repeated a few days or a week and subsequently at intervals of one or two weeks for 3 or 4 doses. The results are usually reactionary at first—sometimes alarming—but soon the fever, etc., subside and the patient begins to improve in a few days. The blood picture shows early improvement, the red cells may double and treble their number in a few weeks, the hemoglobin rapidly rises and the color index approaches the normal. Sometimes a temporary polycythemia picture appears.

It has been our experience at the Royal Victoria Hospital, Montreal, that while improvement occurs the blood picture never attains nearly the normal and that the subjective symptoms are the chief evidences of benefit. Relapses, too, are inevitable though often delayed for even years. No degree of severity contraindicates its use intramuscularly. Certainly the salvarsan is directly responsible for amelioration in many cases though its mode of action is still unexplained. It is of use, too, apart from any history of syphilis.

On the other hand one must remember too the frequent lengthening of remissions by other methods of treatment. In our own series of cases in Montreal one patient showed rapid and marked improvement with dilute HCl and no other drug, another one by rest out of doors, and a third, who had failed to respond to the usual forms of medication, finally developed almost a normal state of health (temporarily) from the encouragement derived by worship at the shrine of modern occultism.

Splenectomy.—Splenectomy is now recommended as the most modern and perhaps the most rational form of treatment. It adds merely another form of symptomatic treatment which has been practiced with increasing frequency within the last three years. Based upon the views of Eppinger and Decastello that the spleen possessed hemolytic properties and that its loss disturbed metabolism and induced nutritive stimulus to the bone marrow, its removal was suggested by them, and the

operation was performed with improvement in the symptoms. Experience had proved that splenectomy for ruptured spleen was sometimes followed by polycythemia, and this fact gave added impetus to the desire to remove the organ in pernicious anemia. The spleen, so to speak, bleeds into its own pulp because of anatomical changes in the vessel walls and thus more and more red cells are destroyed by its hemolytic action. It has not, however, been conclusively proven that this action does occur. It may be that the spleen is but the depository for broken down corpuscles whose constituent elements are being again worked over and prepared for use in the body. Another theory with which splenectomy is concerned is the disturbed function of the organ or its hyperactivity. King, working out the metabolism of the lipoids, has found experimentally that splenectomy increases the total fats and cholesterins and diminishes the unsaturated fatty acids. These latter, however, are increased in the blood in pernicious anemia and induce hemolysis. Hence the benefit of splenectomy.

Roblee believes in the existence in pernicious anemia of a toxin related to the increase of unsaturated fatty acids, and argues that the spleen helps to elaborate these and thus to diminish total fats and cholesterins which are antihemolytic, and that for this reason it should be removed. Ever since Eppinger's original suggestion in 1913, the literature has been replete with more or less commendation of the operative treatment of pernicious anemia. None, however, seem to claim more than an added period of remission, and admit likewise that its rationale is not fundamental. Klemperer and Hirschfeld report 6 cases (including 2 of Eppinger's) in which splenectomy was followed by marked improvement. In 2 of these the blood picture was promptly changed and the circulation was flooded with nucleated red cells suggesting regeneration. Among many writers are Bruhn-Fahrous with 47 collected cases in 1912, and Krumbhaar with 153 cases; while Lee, Balfour, McClure and others reported success. So also did Huber (1 case), Jagie (3 cases), Vincent and Robertson (5 cases), and Giffin. To summarize the results of the experiences of the various writers and that derived from the observation of our own cases we may say:

1. Splenectomy is merely a symptomatic treatment and is not curative.

2. It is an easy and safe operation.

3. The *indications* are that the patient must be still at an early stage of the disease, and his general condition must be fair. Operation moreover is more rational where there is enlargement of the spleen, with urobilin in the urine, an icteroid appearance of the skin, and a red cell count of 1,500,000.

4. The *contraindications*, if any, and the occasions where operation is not liable to meet with success, are acute febrile cases, and those in a chronic advanced stage with marked changes in the cord.

5. Results in favorable cases:

(a) Rapid recovery from immediate effects of operation.

(b) Rapid remissions with marked improvement over long periods of time.

6. Blood destruction recurs showing that the spleen is only partially responsible as an etiological factor in the disease.

(c) The blood picture improves quickly, the red blood cells increase in number, so also do the leukocytes and the percentage of hemoglobin improve. The circulating blood (Port) is flooded with Jolly bodies (nuclear remnants with microchemical reaction of chromatin).

(d) The subjective symptoms of these patients improve remarkably, their digestion improves, their strength returns, and their general appearance is that of better health.

(e) The duration of life is longer.

7. The results on metabolism are not strikingly altered after a few weeks. Dr. E. H. Mason after examining two such cases in the Royal Victoria Hospital found the nitrogen balances unchanged, as did also Pepper and Austin, and that there was at first a temporary nitrogen retention. The uric acid output was slightly diminished, as was also the iron output in the feces, and there was some diminution of the urobilin.

8. Preliminary transfusions are to be recommended.

Our experience at the Royal Victoria Hospital warrants the conclusion that better results are obtained when repeated transfusions are done before and after the operation.

830. Line 2 *read*:

used to save life in the case of acute anemia, **although Folli had used it in 1654 and Denis in 1667 as a life saving method with only moderate success.** Since then from time to

Lines 11-15 *substitute*:

Our studies of hematology and immunity have led to the important observation that blood of different species often varies to such an extent as to render indiscriminate transfusion of great danger to the recipient and, moreover, that in the human subject the variations are such that without previous tests for the compatibility of the blood of recipient and donor, it is impossible to tell whether safety can be assured.

831. Line 3 *add* after "hemolysis.":

There have been various opinions as to why transfusion should be beneficial, and in the estimation of many the mere volume of blood explained the improvement. For this reason it was held that the use of transfusion had no advantage over the intravenous injections of saline solutions. But here again modern hematology has demonstrated that blood formation is stimulated by the introduction of new blood, so that

transfusion has obtained an added importance. After all, the object of transfusion is to attain a safe, rapid and simple mode of restoring the volume of blood, but more especially its regeneration in the blood-forming organs. Intravenous saline injections, however, are useful only where the organs are already in good condition and can withstand the immediate and violent stimulation of a large volume of fluid. The *object* of transfusion, then, is to provide those morphological elements and active principles from the donor which can improve the impaired metabolism of the recipient and stimulate his cells and hemopoietic organs. This is all transfusion is expected to accomplish, for it neither rejuvenates old organs, nor repairs diseased tissues, though it affords them time to regain their loss and to add a stimulus to their new growth.

One must bear in mind, however, that transfusion is no panacea, and that we should therefore avoid too great enthusiasm about its employment, though when properly used, and in suitable cases, it may be of the greatest benefit.

With the improvement in modern surgery and the advantages of asepsis, the manipulation of blood vessels in skilled hands has become a comparatively simple matter, and today, thanks to the genius of Carrel and Crile, the renewed appreciation of transfusion has gained ground. If today appeal is seldom made to their methods (artery to vein transfusion), on the other hand, we are indebted to their zeal for making it more obvious that transfusion is not only a benefit where much loss of blood has occurred, but in many other ways it operates both as a life-saver and a healer of disease.

It must not be supposed from the above remarks that the transfusion from the donor's arteries to the veins of the recipient is by any means an obsolete method, for during the present crisis in France the surgeons are employing this method with success,—witness the brilliant results of Berard and Lumière in September, 1915. There is no doubt, however, that surgical skill and well-practiced technique are essential to the successful employment of artery to vein transfusion and the indirect method of collecting blood from the donor's veins with citrate solutions and in paraffin tubes, prior to the injection, can easily be employed with very little apparatus, with comparatively little skill, and much more expeditiously.

Since the profession at large has begun to favor its employment, many methods have been invented to replace the more difficult and dangerous technique of Carrel and Crile. Lindeman, for example, was among the first to use the vein to vein transfusion in a large series of cases, though von Ziemssen, too, had used it twenty years earlier. The blood is withdrawn by syringes from the veins of the donor, and injected *seriatim* into the recipient. But this method was found rather complex. The need of many assistants and too much and too frequent handling of the

cannulae resulted in jarring, in trauma, and in over-frequent clotting of the blood. Though his results were remarkable, they should be attributed to his individual skill rather than to the method he employed. It was necessary, if possible, to gain some method by which trauma to the vessels and unnecessary clotting could be avoided, so that a large amount of blood could be taken from the donor at one time. This has been successfully accomplished within the last few years, both by the direct and indirect method. Perhaps the greatest achievement is the invention of Unger, who uses the direct method. A short needle attached to a rubber tube is placed in each of the veins of the recipient and donor. These two tubes are severally attached to a double-way stop-cock which, connected with a syringe, alternately withdraws blood from the donor, and then supplies it to the recipient. At the same time there is another syringe attached to the stop-cock which alternately supplies saline to each. When a syringe full of blood has been withdrawn, the stop-cock is turned, thus allowing the blood to be injected into the recipient, while the saline at the same time is made to flow into the tube connected with the donor. In this way both channels are constantly suffused with blood or saline, as the case may be, and clotting is easily prevented. The apparatus is previously washed with a thin solution of paraffin, which further inhibits the clotting. Recently Unger has even dispensed with the paraffin as being unnecessary.

Sixty c.c. of blood can be transfused per minute,—the method is rapid, the speed may be controlled, and the blood is kept outside of the body for a minimum of time, so that clotting is in every way prevented. Unless the patient is very stout, or the veins very small, there is no need to expose them, as the needles may be inserted with ease directly into the veins through the skin.

Another remarkable device (an indirect method) has been perfected in various ways by Kimpton and by Weil.

Kimpton's method consists in the use of large paraffin-coated glass cylinders (250 cm.) with an exaggerated S-curve at one extremity which is drawn to a fine point, allowing its insertion into the vein. The blood is collected from the donor's vein and subsequently expelled into the recipient's vein by means of a rubber bulb. The paraffin coating delays coagulation, and allows a reasonable interval to elapse before the blood is injected. The disadvantages of this method, however, are obvious. It is not always easy to withdraw the blood in this way from the donor's veins, and later even when the tube has successfully been filled, any accidental clotting at the point of the tube would render useless the large quantity of blood withdrawn.

Hierudin, which is an active principle from the buccal gland of the pond leech, is sometimes used instead of paraffin to minimize the danger of coagulation. The method was devised by Satterlee and Hooker, but

Lewison's experience indicates that its employment is dangerous. Its anticoagulant action is attributed to its power to effect balance between the prothrombin and antithrombin, or at all events to neutralize the thrombin and the prothrombin.

Line 6 *add* after "obtains.":

By this method the blood having been withdrawn from the donor is deprived of its fibrin through stirring and thus injected into the recipient. There is no doubt that in the past many successful transfusions have been made by this means, despite its present unpopularity. Those who are opposed to this method hold that as the fibrinogen and platelets are removed and the cells injured, much of the value of this method is lost. Possibly the patient's antithrombin may not be sufficient to counteract the effect of the thrombus in the defibrinated blood, and intravascular clots may result.

832. Line 25 *add* after "months.":

Among the most illuminating records of the effects of transfusion are those of Ottenberg and Libman; 212 transfusions were done in 189 patients with various forms of blood disease. In 42 the transfusion was done to save life with very excellent results. Twenty-five cases of pernicious anemia were treated; their results show that while transfusion is not curative, it overcomes the anemia better than other measures, that remissions are more decided and the subjective sensations improved. The amount injected is not of essential importance and in their opinion 500 to 1,000 c.c. usually suffice.

Of the *dangers* of transfusion much has been written. Blood is a complex tissue and the changes in its quality and quantity are numerous under many conditions. The ideal to be attained is to give to the receiver a blood which is both acceptable and potent, and so to modify the donor's blood as to attain this end. The incompatibility presents one of the greatest dangers, particularly from hemolysis, though it has been questioned whether or not this danger is over-estimated. Considering the amount of transfusion done, and the frequent disregard of this danger, it may be said that disastrous results are few. It should be remembered that from small causes the donor's blood, previously compatible, may easily be rendered incompatible, as, for example, by the taking of alcohol. Further, that blood may not hemolyze *in vitro*, but may do so in the circulation, and vice versa.

It was Bernheim's impression that where urgency was required it was not worth while attempting the test for hemolysis, and more recently Berard, who, during the present war, has employed transfusion with and without the hemolysis tests for a large series of cases in which clots, infections, pyrexia, and other serious conditions were present, has pointed out that not a single instance of trouble from this source was observed. It is, of course, of great importance during the operation to avoid the

admixture of any thromboplastin from wounded tissue of the donor's vessels, as well as of the thromboplastin which might be derived from the cells of the blood through friction during the transfer.

Notwithstanding the recorded successes in this field, it must never be forgotten that one is constantly confronted with this danger, and that a hemolysis may occur and has indeed occurred with hemoglobinuria and other serious symptoms. For this reason one is not justified in omitting the tests, where time permits.

The danger from air embolism seems equally exaggerated; at all events air purposely introduced into the veins of lower animals, during experimental transfusion, produced no serious results.

Dilatation of the heart as a result of transfusion is an easily avoidable consequence when any of the modern methods is employed. By any of the means above mentioned the quantity of blood and the speed of its transfer can be easily regulated to suit the requirements of the participant.

Our own experience as to the *beneficial effects of transfusion* in pernicious anemia leads us to conclude that it sometimes is of distinct value, and, if repeated, may confer very great benefit upon the patient. The subjective symptoms improve, the appetite returns, the dyspnea becomes less marked, the fever diminishes, and the general strength may return almost to the normal. Remissions, however, are of variable duration and no permanency of cure has so far resulted, even where repeated injections of blood have been tried. Transfusion is not a curative measure, for it does not reach the cause of the disease. It is therefore only a symptomatic therapy, but as such it is of great value.

836. Line 2 *add* after "substances":

(For the investigations of Pringsheim and others on cholesterin in paroxysmal hemoglobinuria *see* Chap. III following—Hemorrhagic Diseases.)

Line 33 *add* after formula:

Hurter prescribes bone marrow in support of other measures in the form of tablets, as follows:

Marrow	90 parts
Port wine	30 "
Glycerin	30 "
Gelatin	20 "

Mix the marrow and wine in one hot mortar, the glycerin and gelatin in another, and then combine and form in tablets. They will keep for months.

Line 35 *add* after "visible":

Pancreatin.—On the theory that the same principles hold good in the organism in relation to immunity as to protective ferment, and arguing from the facts that diphtheria antitoxin contains an increasing amount

of antitrypsin with increasing immunizing power, and that an unusually high antiferment content of the blood is an important feature of exhausting diseases, Brieger proposes the possibility of restoring normal relations in pernicious anemia by the administration of pancreatin. He treated three cases by combining this with arsenic, giving the pancreatin before and liquor arsenicalis after meals. Rapid improvement followed with a rapid drop in the antitrypsin content of the blood. The results were not permanent, however, two of the patients having died since of the disease. The third has been under observation three years.

838. Add under "References":

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CHAPTER II

LEUKEMIA AND HODGKIN'S DISEASE

C. F. MARTIN

847. Line 17 *add* after "given.":

The modern treatment demands the use of three methods:

1. The use of radioactive elements.
2. The use of benzol.
3. Arsenical treatment.

Line 18 *read*:

Arsenic.—Very few drugs seem to have even a temporary

Line 32 *read*:

Naphthalin Tetrachlorid.—Drysdale has recently recorded a rather remarkable improvement from

848. Lines 4-7 *substitute*:

Radiotherapy.—*Historical Note.* The treatment of leukemia by X-rays emanated in the first place from America, where the first application was made by Pusey in 1902. In the following year Senn reported two cases, one of leukemia and one of pseudoleukemia, with marked improvement. Skepticism was at first shown in Germany, until Krone and Ahrens published successful cases in 1904. Full studies of the histological appearances and changes in metabolism were made by Krause, Heinecke and Ziegler. A wealth of literature followed.

Line 34 *add* after "IRRADIATION.—":

Several theories find acceptance. Of these only two need mention. *The cellular theory*, supported by Grawitz, Barmon and Linser, Mosse, Ziegler, Krause, Tatarskey and Wolby, and others, is based on the changes in lymphoid tissue taking place after irradiation, such as rarefying of cellular structure, hypoplasia of follicles, etc. The X-rays are claimed to have a definite specific action on lymphoid tissue everywhere, the bone marrow being affected last. This theory is probably, at least in part, true.

Line 38 *add* after "distintegration.":

Upon normal individuals Demieville found that irradiation reduces the number of white blood cells by 400 to 1,000 per cm.

The effect is complex, depending on various conditions, namely,—the dose, the region and surface irradiated, the individual susceptibility, and the state of the individual's hemopoietic organs, especially his lymph glands. One irradiation of half an erythema dose on an indifferent region causes leukopenia and cell destruction. Repeated and fractional doses cause hyperleukocytosis, according to area treated, and later young forms appear, some of which are abnormal degenerated cells, while later still myeloid reaction occurs, especially when myeloid tissue is irradiated, and this reaction seems to lessen with each subsequent treatment. Eosinophiles reach their minimum in four days. Red blood cells vary little, at first increasing slightly and then diminishing in number. The hemoglobin slowly lessens in percentage. Cells become degenerated in the circulation, but Warthin's researches on tissues irradiated show that leukocytes degenerate even till their number is subnormal (aleukia) and then a limit is reached or an adaptation attained, with changes in the hemolymph glands and bone marrow. A lower type of leukoblastic tissue is developed with more primitive but more resistant cells. He concludes that the action of X-rays is degenerative and inhibitory but not curative, the essential leukemic process not being thereby arrested.

Lines 40-41 *read*:

proved that X-rays killed the experimental animals by complete **destruction of the cells in the** blood-forming organs and leukocytes in the blood, while

849. Line 22 *add* after "phenomena.":

It does not seem that there is an elective destruction in the circulating blood of the lymphocytes. On the contrary the difference in effect on the two systems of hemopoietic organs seems to come from filtration of rays through to the bones.

850. Line 33 *read*:

Hence arose the idea that the effect of X-rays is to produce specific leukotoxins, which are **generated by the dying leukocytes and are diffusible throughout the body.** The leukotoxin theory is rendered doubtful by the work of Klieneberger, Zöppitz, and Krause, who worked with every facility for bacteriological technique, but could not prove to themselves that even prolonged irradiation produced a Röntgenitic leukotoxin. Yet it would seem that some indirect action (perhaps through products of decomposition) on the hemopoietic organs occurs when these organs are subjected to X-rays.

852. Line 11 *read*:

in size, the **hemoglobin rises and the red corpuscles are usually markedly**

increased, the leukocytes fall (in 92 per cent. of cases, Krause) and the qualitative blood picture improves, the myelocytes becoming greatly reduced and the polynuclears relatively increased, giving rise to what is known as the latent period: the rise in weight is constant, giving rise to what is known as the

Line 15 *add* after "affection.":

Of 187 cases of myeloid leukemia treated, 141 were much better after irradiation, and the improvement lasted for several years—the longest seven years. The remainder, chiefly old cases, were refractory.

Line 38 *add* after "lessened.":

In chronic lymphatic leukemia the results are often striking, the glands often being reduced to the normal in two or three weeks. The leukocytes are markedly reduced, but again it is a quantitative rather than a qualitative change, for the lymphocytes remain relatively increased. Death may be delayed three to five years.

Line 43 *read*:

ation in technique exists. As a rule hard tubes are employed; **a hardness of 6-7 is said to be best, measured on the Walther scale.** Tubes of greater hardness cast sparks and alarm the patient, if too soft they are injurious to the skin. When a soft tube is used, the skin should be protected by an aluminum (0.5 to 1 mm. thick) or silver filter. Even with the hard tube when prolonged irradiation is applied, a filter of tissue paper, linen or chamois should be employed, and the adjacent surface should be protected by "blendenpaste"; burns are

853. Line 7 *add* after "accuracy.":

Krause recommends $\frac{1}{2}$ to $\frac{1}{4}$ the "erythema dose" at one sitting, two or three times a week, the total dose given to about equal 5 erythema doses.

Line 44 *add* after "tissue.":

Thorium-X.—The therapeutic researches of Bickel and others with this radioactive element will be found under Pernicious Anemia, Chap. I, this section. Its effect upon the cellular elements of the blood is similar to that of radium, as set forth in the preceding paragraph. To produce a reduction in white cells, such as is attempted in the leukemias, it must be given in much larger doses than in the anemias, where the aim is simply to stimulate the bone marrow to an increased red cell formation, and where, especially in the case of the pernicious form, large doses are both useless and dangerous. In leukemia, on the other hand, especially the myelogenous form, or in lymphomatous tumors, the treatment should be initiated by one or two large intravenous injections of one to three million Maché units, followed later by daily doses by the mouth, say, of one million Maché units. This treatment can be continued over some months (Bickel) without untoward effect, and has in the hands of several observers, Bickel,

Klemperer and Hirschfeld, Grund, Nagelschmidt, led to marked symptomatic improvement, similar to that produced by irradiation.

The Benzol Treatment.—It seems to have been Barker's discovery of the destructive action of benzol upon the blood and Selling's subsequent work on this subject which led Koranyi (1912) to use it in the treatment of leukemia and polycythemia, and subsequent observers have confirmed the efficacy of the treatment beyond any which has since been employed. Time, however, has yet to prove whether the treatment is of permanent value.

The *method of administration* now in vogue is usually that of Kiralyfi's. Benzol is combined with olive oil as recommended by Koranyi in doses of $\frac{1}{2}$ gram in pearls. Four pearls are given on the first day during food; six on the second; eight on the third day; and ten on the fourth and subsequent days. One must begin always with small doses, gradually raising the amount, while carefully watching the progress of the disease and condition of the blood. The individual susceptibility is decided in this way and one must proceed carefully, for latent periods often exist during which the effect of the drug is apparently nil. One should continue the use of benzol unless the white blood cells remain at a stage much above the normal, or rise again in the course of the treatment.

The treatment should never be continued up to the time when the white blood cells become normal, for the effects of the drug are seen for some period after the last dose has been administered. The temperature, pulse, digestion, and general condition of the patient should be carefully observed and the urine repeatedly examined.

The advantages of the drug are as follows: It is cheap; it is easily used; powerful in its action though not radical in its effects. It produces no dermatitis, while yet it diminishes the white blood cells of the embryonic type, though not those of the ordinary type. The size of the liver and spleen, and glands, diminishes under the treatment. In other words, it acts very much in the same way as X-rays, and sometimes its effects are more permanent, though more slow.

Most observers agree that it is well to *combine the benzol treatment with radiotherapy*, and, moreover, that arsenic and iron should be used in the treatment just as in ordinary methods.

Duration of the treatment varies according to circumstances from three weeks to four months. Periodic courses of treatment must be undertaken.

Molezanow has treated five cases, with excellent results in four. He has shown that the hemoglobin and the red blood cells fall, to rise after a period of a week or so, and, vice versa, the white blood cells may rise during the first week and then diminish, and that the same is true in the case of the spleen and lymph glands, which at first may increase in size and then diminish after one week. The myelocytes in his cases dimin-

ished in number while the polynuclear cells were increased. His conclusions were that the benzol destroys the pathological leukocytes, hence the leukopenia. Results of his cases showed improvement in sleep, in weight, strength and appetite, and pains in the bones were relieved. There were no relapses.

Liachowsky, Demidow, Lutschewski and Kiralyfi all record cases that showed favorable results, while Turk reported one unfavorable one in which the treatment of radiotherapy succeeded better than did the benzol.

Billings was the first authority in America to apply the benzol treatment in leukemia. His results in the five cases reported are rightly described as phenomenal. All the patients but one had previously received X-ray treatment. The benzol was usually given in gelatin capsules filled at the time of administration, beginning with seven minims and ascending to fifteen minims, three or four times daily. In all the cases there was a rapid fall in the leukocytes, amounting in three instances to a leukopenia, and preceded in two by a temporary rise. The qualitative blood picture, however, presented a *bizarre* mixture of many pathological types of white cells, and did not return to normal. In the four myelogenous cases, the red cell count and hemoglobin improved. In all five cases a rapid diminution in the size of the spleen occurred, much more marked than is usually seen under exposure to the X-rays, and in the one case of lymphatic leukemia, there was a rapid reduction also in the multiple enlarged lymph nodes. He points out that benzol, while a remedy of much promise in leukemia, should be used with caution, as its effect in large doses is certainly to render the bone-marrow hypoplastic, and the danger of inducing an aplastic anemia should therefore always be kept in mind. Only the pure drug should be given, as impure benzol contains anilin and other toxic products.

Moorhead testifies to the efficacy of benzol in one cases of "splenomedullary" type, and notes the suddenness of the drop in white cells (132,500 to 76,000 in three days), further the marked change in the differential white cell count. Prior to treatment, myeloblasts and myelocytes dominated the picture with 45 per cent. and 10 per cent. respectively, while neutrophiles were relatively diminished (32 per cent.). Three months after benzol had been administered the differential white cell count had returned to normal, while the red cells and hemoglobin had also vastly improved. He had less success with a case of lymphatic leukemia though, temporarily, benefit accrued.

Pappenheim looks with less favor on the benzol treatment and regards the dosage as too small to be effectual in depressing marrow cell formation. The leukopenia, he says, is only apparent, the polynuclear cells being stowed up in the internal vessels. Sohn came to the same conclusion after a study of the metabolism of benzol administration. Large

doses were found to be dangerous, leading to diminished oxidation processes, acidosis and toxic necroses in the liver and kidneys.

Muhlmann's experience confirms these observations, for a fatal result in a case of lymphatic leukemia followed the administration of 175 gms. of benzol in six months. Extensive necroses were found in the liver. Pappenheim tried benzene and found it to be equal in power to benzol and less injurious, though both were regarded as inferior to radioactive substances, and the results showed that they were neither so elective, nor radical, nor constant in their effects on the bone marrow and the hemopoietic apparatus.

Thorium, however, was found to be more potent in driving leukocytes entirely out of the peripheral circulation. Weiskotten, Schwartz, and Steensland studied the action of benzol on various groups of animals with and without splenectomy and found a temporary fall in the polynuclear leukocytes of the peripheral circulation, which they ascribed to a toxic effect.

Summary.—Our own experience has shown that benzol is a very efficacious remedy in myelogenous leukemia, reducing the size of the spleen and the number of leukocytes and improving the general condition of the patient. This improvement is only temporary, the remission lasting a varying time up to several years. Ultimately the disease leads to a fatal issue. Sometimes the relapses are very sudden and the type changes to that of the acute lymphatic form.

Lymphatic leukemia is less influenced by benzol, but experience shows that some cases are apparently benefited by its use. Benzol indeed is ineffectual in many cases of both varieties, and experience has shown that the X-rays will often initiate an improvement where benzol has failed. Our own practice is to use them both combined. Benzol may be given in gradually increasing doses commencing with 5 to 7 drops with equal parts of olive oil, in capsule, three times a day, increasing daily by one drop till fifteen drops three times daily are used. At the same time the X-rays are used on the different parts of the hemopoietic system chiefly over the long bones and the spleen, not oftener than three times weekly. Turk and others have found cases benefited, first by the use of one method, later by the other. In one case the patient progressed favorably on X-rays alone for a time, and the treatment was then changed to benzol without effect. Recourse was then had to X-ray again with renewed benefit. In one case of chronic lymphatic type benzol was found to be useless, where the X-rays later gave great benefit. In Jespersen's case, which was of the myelogenous type, the X-ray proved useless after two courses and benzol later on proved beneficial for a time. Krokiewicz found benzol safe and not cumulative; doses larger than three gms. daily caused digestive disturbances and albuminuria.

The effects on the blood vary greatly in different individuals. The

leukocytes do not always numerically decrease and the relation of the types of leukocytes sometimes remains as before. The effect on the viscera varies with the different cases, and no general law will be found to apply to the effects of treatment in all cases.

More often polynuclear neutrophiles remain unaltered while the abnormal granular cells may diminish out of proportion to the other forms, then after a short time the preëxisting relations return.

854. Line 13 *add* after "tumor." :

In general it may be said that the treatment of Hodgkin's disease is unsatisfactory in the majority of cases, although cures have been recorded lasting over a period of 6 years, and the future would seem to be bright under modern research in treatment of this disease. The X-ray formed a prominent part in the treatment of those cases. The results vary perhaps according to one's conception of the disease. Bunting and Yates lean towards the microbic origin of the disease and have described a polymorphin diphtheroid organism against which the body, as a rule, is unable to produce enough antibodies to overcome the infection. Some skepticism has been expressed as to the validity of this discovery. Mallory regards the disease as essentially neoplastic, not infectious, while J. H. Wright and others lay stress on the presence, normally, in the lymph nodes, of similar bacteria. Again authors describe bacteria present also in this disease and associated with this diphtheroid organism, e.g., streptococci, staphylococci, *B. Welchii*, etc. Sources of infection were looked for and the organisms were found in the tonsils and in alveolar abscesses. It is also striking on the other hand that the organism of Bunting and Yates has been found in lymphosarcoma. It is for these reasons that the efficacy of the vaccine produced with aërobic and anaërobic cultures, and which seem to have been followed by successful results, is to be ascribed to the concomitant treatment.

Their procedure is briefly as follows:

1. Tonsillectomy to remove a main portal of infection.
2. Excision of as much diseased tissue as possible.
3. Bathing the wound in iodine to prevent recurrence.
4. X-ray treatment commenced a few hours later.
5. The specific treatment by means of injecting serum or vaccine prepared from aërobic and anaërobic cultures.
6. General hygienic measures.

The success of this treatment depends, they say, on the absence of a periadenitis. Out of ten cases two were cured, up to 5 and 6 years' observation. Four others are doing well and are looked upon as ultimate cures. The remainder have not done well.

Realizing the benefit derived from X-rays alone one would seem to be scarcely in a position to attribute the success of these cases to the specific treatment *per se*.

Herbert French has experienced good results from the use of large doses of radium applied locally. T. R. Brown had remarkable results in two cases with only two applications in very large doses (200 milligrams) (personal communication).

Line 20 read:

Arsenic is still of importance in the treatment. It is worthy of note that some of the

854. Add under "References":

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CHAPTER III

HEMORRHAGIC DISEASES

C. F. MARTIN

858. Line 17 *read*:

(Schonlein). **The term applies more to senile forms (Batemann) but is confusing.** In still another set of symptoms the purpura arises

859. Line 14 *add* after "urticans.":

Pathogenesis.—Since the interesting researches of Duke and others it has been generally conceded that purpura is directly associated with a deficiency in blood platelets. Normally about 200,000 to 400,000 exist in the blood to each cubic millimeter, while in purpura hemorrhagica there may be 10,000 or even less ("essential thrombopeny"). It is perhaps still uncertain whether this be the cause or effect of the disease and it is not decided to what extent changes in the vessel wall may contribute to the picture. The platelets or some substances produced by them are important where irritant chemical or bacterial toxins enter the blood stream. During normal coagulation platelets disintegrate. In hemorrhagic diseases they should form a nidus from which fibrin extends in the formation of a clot. No doubt other changes occur too, and we have to do with the amount of circulating antithrombin, prothrombin and calcium, but the exact disturbance is still unknown. We do know that in purpura hemorrhagica a clot does not retract, and that it does not extrude serum. Further, that the coagulation time is not prolonged (thus differing from the hemophilic state), and lastly that the bleeding time of a needle prick is lengthened.

Line 24 *add* after "avoided.":

In the treatment of purpura as in all the hemorrhagic diseases, the methods of transfusion and of serum therapy are of paramount importance.

Serum Therapy.—Treatment is directed towards supplying the required elements to make up for the deficiencies in the blood mentioned above and various means are employed.

COAGULEN.—(Kocher-Fonio) An extract of animal blood platelets pre-

pared as a yellow powder soluble in water is used intravenously and subcutaneously; 1 gm. in 10 c.c. aq. dest. supplies one of the defects, but lacks the freshness of ordinary serum (Halpen). It is of greatest use as a *local* styptic. Frank centrifugalized human blood plasma, extracted the blood plates and used them locally and intravenously with good results.

TRANSFUSION.—Transfusion (*see* pernicious anemia) supplies the defective substances and has the advantage of freshness, but requires preliminary tests and is therefore time taking. Ottenberg and Libman, however, had success in 9 cases thus treated.

WHOLE BLOOD.—Much has recently been written of this method. Emsheimer used it subcutaneously and intramuscularly in doses of 20 c.c., and obtained rapid improvement. He finds the method simple, safe, effective, with no untoward effects. Howard has similar results (28 to 90 c.c. in 4 injections over 6 days) and Jarvis in the pediatric clinic at Hartford prefers this to all other methods. He takes the blood from a convenient vein of some relative, and by means of a record syringe injects 10 to 20 c.c. into the buttocks of the child, repeating it in 4 to 6 hours.

Normal serum of horse or rabbit has given excellent results. As a rule 10 to 30 c.c. may be given subcutaneously, or less intravenously (10 c.c.), and repeated if need be every 4 to 6 hours. Anaphylaxis is avoided if the injections are repeated within 10 days. There is no danger of this with human serum. If repetition is needed the animal must be changed (*see* article on hemophilia). Bodenheimer used two injections intramuscularly of 10 c.c. of horse serum with success, and many others have had similar results. The writer can testify to its benefits in a number of cases, and would recommend larger doses—say 20 c.c.—repeated on several successive days. Schleuler recently cured a severe case with injections of 10 c.c. daily for 10 days (100 c.c.) and such is to be accepted as the most satisfactory means of cure. (For further methods of treatment *see* under hemophilia.)

860. Line 20 *add* after “jaundice.”:

Two conditions are recognized under the title of hemorrhagia neonatorum, the one associated with syphilis and sepsis, the other a distinct entity in that so far no etiology has been found. To the latter has been assigned the name *morbus maculosis neonatorum*.

TREATMENT

Two forms of treatment have been recommended, the one by *serum injections*, which as a rule is most satisfactory; the other by *indirect transfusion*. The former is preferable as being more easily carried out, for indirect transfusion is difficult in these cases on account of the infantile condition of the patient. Lespinasse had 13 recoveries out of 15

patients with hemorrhagia neonatorum treated by direct transfusion. (For details of these two forms of therapy *see* under hemophilia.)

861. Line 16 *add* after “-lation.”:

Recent observers insist on a deficiency of prothrombin as a constant characteristic (Howell). Hurwitz and Lucas, studying problems of blood coagulation in hemophilic states, conclude that the reaction of hemophilic blood is normal, and that while coagulation is delayed the clot once formed shows normal retraction. Further that circulating prothrombin is the essential defect, while the other two factors in clotting, namely, antithrombin and fibrinogen, are normal.

Line 17 *read*:

thrombokinas, **a film forming substance** secreted by the vessel wall, as Sahli thinks, or whether,

Line 31 *read*:

calcium content, **and especially if the blood loss be excessive.**

862. Line 20 *add* after “necessary.”:

Calcium may be used in the form of lime water, $\frac{1}{2}$ oz. three times a day in milk, or water will suffice. It may or may not be used in the form of the lactate, five gms. t. i. d. Calcium chlorid, which is used in the same dose, well diluted, may be given, though it is apt to irritate. It has no advantage over the other forms.

865. Line 44 *add* after “results.”:

Jennings reports cure of the hemophilic state in an infant of four days by two injections of normal horse serum, 8 and 7 c.c. respectively, given at 9 hours' interval. Similarly Clough controlled the situation in a hemophilic girl of 14 in whom ergot, stypticin, calcium chlorid and gelatin had been given without result. Thirty c.c. of horse serum was injected, and three months later treatment was continued by injections of the mother's blood repeated at three months' interval. Traver reports immediate results from the subcutaneous injections of human blood serum in a boy of 5 who bled for six days from a slight cut on the tongue. The blood from his father was placed in the ice-box for ten hours, and 20 c.c. of the serum thus obtained was injected subcutaneously into the buttock. Immediate clotting (within 20 seconds) took place over the wound. The injection was repeated twice at 8 hours' interval. Successful series of cases are also reported by Nicholson, Reuben and others.

866. Lines 4-15 *substitute*:

Transfusion for Hemophilia.—(*See* Pernicious Anemia for details.) This method is of comparatively recent date for the treatment of hemophilia, and, although its use has not been so universal as that of horse serum, many successes have been recorded. Vincent used direct transfusion in 11 cases and cured 8. Ottenberg and Libman treated 5 cases

successfully and suggest that every hemophilic should have donors ready whose blood is known to be compatible.

Line 18 *add* after "transient." :

On the theory that prothrombin is deficient in hemophilia, one may attempt to treat by adjusting the prothrombin-antithrombin balance by introducing thrombin or prothrombin into the circulation or by stimulating the tissues to produce more thrombin, or again by neutralizing relative excess of antithrombin by injecting tissue extracts. Brain lipoid has been found to be a useful source of fibrin ferment, and a diphosphate, *kephalin*, present in brain tissues and extracted with ether, has been used in hemorrhagic diseases, and is most efficacious as a local hemostatic. Its action on normal animals is to cause temporary coagulation, while in hemophilics the action is more permanent. Hurwitz and Lucas commended its use especially as a local hemostatic in capillary oozings.

Line 33 *add* after "malady." :

Coagulose (P. D. and Co.).—Coagulose, an anhydrous powder, sterile and soluble, containing fibrin ferment for clotting blood, is now much in vogue. It is supplied in bulbs; contents of one bulb are dissolved in 6-8 c.c. of sterile water, well shaken, and injected (Collander). Tallant records successful use of the drug.

867. Line 27 *add* after "Fenwick." :

CHOLESTERIN IN PAROXYSMAL HEMOGLOBINURIA.—Meyerstein showed rabbits which had been saturated with cholesterol remained without reaction after intravenous injections of soap solution, while in the control rabbits (not treated with cholesterol) soap solution produced hemoglobinemia and hemoglobinuria. Kurz and Grimm cured several cases of black water fever which had run their course under the form of a cyclic recurrent hemoglobinuria by the internal administration of cholesterol. On the ground of such observations and because of the known action of cholesterol in stopping the hemolytic process *in vitro*, Pringsheim treated a case of paroxysmal hemoglobinuria under his care by daily intramuscular injections of .5 gram cholesterol in 10 per cent. emulsion of physiological salt solution. The attack was frustrated, the chill and fever occurring, but no blood appearing in the urine; after stopping the injections the sensibility to cold returned. An explanation of the action of the cholesterol upon these cases is not attempted, but the conclusion lies near that the same process is at work *in vivo*, in the arrest of hemolysis, as occurs when cholesterol is added *in vitro*.

Radium.—The action of radioactive substances upon the cellular contents of the blood, and their therapeutic possibilities in this connection, have been mentioned under Anemia and Leukemia, in this section. The further effect upon the body ferments was one of their earliest bio-

logical properties to be known, and has been made the subject of extensive studies by Lowenthal, Bickel, Weil, Wohlgemuth and others. Thus Lowenthal and Wohlgemuth found it accelerated the action of the diastatic ferment in the blood, bile, saliva, and pancreatic juice in a large number of cases, the acceleration being preceded by a temporary inhibition. In some cases only the inhibitory action was apparent, the variation probably resulting from a variation in the strength of the emanation, or in the concentration of the ferment solution. These observations were applied by von der Velden to the problem of shortening the coagulation time of the blood, on which he found that radium, like peptone and other bodies, has definite effect. It has been established by him by experiments, both *in vitro* and *in vivo*, as well as by clinical observations, both in the normal subjects and in two cases of hemophilia studied, that radium emanations, whether given by the mouth or by inhalation, shorten the coagulation time to an appreciable extent. The effect is transitory, passing off with the emanations. The mode of action is not by any means understood, for the combination in which the emanations exist in the blood is not itself established. It may act directly by replacing or assisting the activating principle thrombokinase, or (following the chemical theory of coagulation) by acting as thromboplastic substances do, by hastening the reaction, or indirectly by causing the passage of lymph from the adjacent tissues into the blood stream by reason of the sudden physical or chemical changes induced. In any case the observation that radium shortens the coagulation time of the blood is definitely established, and in the further development of our knowledge of radioactivity, this fact may be found to have a definite bearing on the treatment of the hemophilic state.

Line 41 *add* after "pulverized.":

Schloessmann advocates the local use of sterilized tissue extracts, such as may be obtained from parenchymatous hyperplastic goiter, and considers these to be at once the most harmless and the most useful local hemostatic known.

868. Line 5 *add* after "requires.":

Sayer used his own blood, obtained by cutting his finger, locally to a wound on a hemophilic boy's forehead, which instantly stopped bleeding. Bluhdorn used with success fresh sterile human serum on a tampon to the wound, as well as injections at its border, in a case of melena and purpura with hemorrhage from the cord in pernicious jaundice of infancy.

870. Line 12 *add* after "vasoconstrictors.":

Howell suggests testing all bloods prior to any operation on patients exhibiting a hemophilic tendency. The blood is first oxalated and then recalcified with an optimum amount of calcium.

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CHAPTER V

BLOOD DISEASES WITH CYANOSIS

C. F. MARTIN

877. Line 26 *add* after "1911.":

Geisbock's disease is the name given to a condition of splenomegalic polycythemia with hypertension, and which Senator, himself, recognized as a variety of the disease (polycythemia hypertonica). A classical description of the two forms is given by Monro and Teacher.

878. Line 28 *add* after "cause.":

Wagner reports three cases of polycythemia, two of which were associated with splenomegaly, in which repeated venesection with removal of 300 to 350 c.c. of blood was practiced with good effect upon the subjective symptoms, especially the very severe perspiration.

Line 32 *add* after "results.":

Weber recommends these measures as palliative in the secondary polycythemia with cyanosis of chronic heart disease.

880. *Add* under "References":

POLYCYTHEMIA WITH SPLENOMEGALY

Monro and Teacher. Three Cases of Polycythemia, 1913, I, p. 1015.

Wagner. Venesection in Polycythemia, Münch. med. Woch., No. 60, 1913, p. 408.

Weber. Secondary Polycythemia and Heart Disease, Arch. d. Mal. du Cœur, April, 1913, p. 225.

CHAPTER VI

DISEASES OF THE ADRENALS

FREDERICK FORCHHEIMER

883. Line 39 *add* after "issue.":

[The use of tuberculin, hypodermically for diagnostic purposes, in Addison's disease is very dangerous to life. I have observed three deaths within twenty-four to forty-eight hours, from acute disseminated tuberculosis, after the use of one to three milligrams of old tuberculin. In all of these patients, Addison's disease was plainly evident. It was very unwise to use tuberculin, to attempt to prove the cause of the disease of the adrenals, because if proved the indications for treatment would not be changed. Syphilis may cause disease of the suprarenal glands and may cause typical symptoms of Addison's disease. A Wassermann blood serum test should be made, therefore, in the case which presents evidences of lues. Active antisiphilitic treatment has been followed by recovery in a few patients with Addison's disease due to syphilis.—EDITOR B.]

CHAPTER VII
DISEASES OF THE SPLEEN

FREDERICK FORCHHEIMER

890. Line 9 *add* after "cures." :

[Splenectomy, first advocated by Banti in splenic anemia, has been adopted by many clinicians as the most promising treatment of pernicious anemia. As in Banti's disease, splenectomy is advocated in pernicious anemia, upon the theory that the toxins elaborated in the spleen are hemolytic substances. Inasmuch as pernicious anemia is a complex pathological condition in which, apparently, several cytotoxins take part in destroying the blood cells, the cells of the mucous membrane of the stomach and small intestine and in many patients the nerve cells of the spinal cord, it is difficult to explain a rational basis for splenectomy in pernicious anemia.—EDITOR B.]

CHAPTER VIII

DISEASES OF THE THYROID AND PARATHYROID GLANDS

FREDERICK FORCHHEIMER

894. Line 24 *add* after "disappointing.":

[Two of the most serious instances of hyperthyroidism that we have seen occurred in patients following the administration of thyroid extract for the treatment of supposed simple goiter. If patients suffering from goiter are given thyroid extract at all, they should be under constant and intelligent supervision.—EDITOR I.]

895. Line 21 *add* after "secretion.":

[Various iodins containing compounds such as the iodothyroglobulin of Oswald have been obtained from thyroid tissue. Recently Kendall has isolated a crystalline iodine-containing compound, which, when given in small doses, gives rise to symptoms resembling those of hyperthyroidism.—EDITOR I.]

896. Line 36 *add* after "symptoms.":

Of late evidence has accumulated which suggests that infections of various sorts apparently may precipitate an attack of hyperthyroidism. While the occurrence of infectious processes in persons suffering from hyperthyroidism in severe instances is probably only a coincidence, it is a fact that in many cases the symptoms of Grave's disease have developed so promptly after acute infections that the possible relationship of the two demands consideration. The relation of previous infections to hyperthyroidism was remarked by French writers years ago. The possibility of infections, either acute or chronic, precipitating or accentuating the symptoms of Grave's disease should be borne in mind. Patients who exhibit the milder symptoms of the partially developed disease should be carefully examined for evidences of chronic infections. The tonsils, teeth and sinuses should be examined and measures should be taken to eradicate any infections found.

902. Line 5 *read*:

only a part of the **thyroid** gland and, therefore, has not the same effect

917. Line 22 *read*:

to have been **used with reported success.**

Line 41 *add* after "organ.":

Serious fall of systolic blood pressure may occur with the usual dose of any pituitary gland. One should not use the preparation without due care and frequent observation of its effect on blood pressure.

919. *Add* under "References":

Kendall, E. C. Jour. Amer. Med. Ass., 1915, LXIV, 2042.

VOLUME IV

DISEASES OF THE KIDNEYS

CHAPTER II

NEPHRITIS

JOSEPH L. MILLER

14. Line 33 *add* after "tubules.":

Recently the strictly selective action of renal toxin for certain structure of the kidney has been questioned; diffuse involvement is the rule. Aschoff reports that Baehr has been able to produce a glomerular nephritis with uranium nitrate.

18. Line 38 *read*:

under discussion but clinical observation on the whole has failed to support his theory. That a moderate degree of acidosis is present in severe nephritis has been shown by Peabody and others. This is due probably to an inability of the kidney to eliminate the normal amount of acids formed in the body, rather than excessive acid production, although Mesenthal has shown that moderate increased protein catabolism may occur in nephritis and thus possibly account for some slight increase in acidosis.

21. Line 17 (B. F.) Line 18 (F.) *read*:

chlorid have been unsuccessful. **Hewlett reports malaise and headache after massive doses of urea.** It is true that in nephritis the urea is not

Line 27 (B. F.) Line 29 (F.) *add* after "rôle.":

Foster and others believe that the various clinical types of uranium may be due to different causes. Where headache and apathy predominate, nitrogen retention is present. Where edema is marked chlorid and water elimination is markedly impaired. In the convulsive type he has isolated a substance from the blood, not urea, with which experimentally he has produced convulsions.

24. Line 40 (B. F.) 25. Line 17 (F.) *add* after "purpose." :

This method has withstood the test of time better than any previous one and its accuracy has been confirmed since the introduction of the blood urea determinations.

25. Line 10 (B. F.) *add* after "function." :

Recently, however, less attention has been paid to delayed secretion, the total amount eliminated in the two or three hours being most important.

Line 18 (B. F.) *add* after "hour." :

Another patient who eliminated 40 per cent. in two hours, 48 hours later developed uremia, and a patient with 17 per cent. in two hours and suggestive uremic symptoms cleared up. Mayo reports two cases with an output of 70 per cent. where uremia developed after an operation. This, as other functional tests, often shows very little variation from the normal in chronic interstitial nephritis.

Line 19 (B. F.) *add* after "present." :

Baetjer has shown that during the stage of acute nephritis there may be marked impairment in the elimination of one substance and normal elimination of others. For this reason any single functioning test may be insufficient.

Line 31 (B. F.) *add* after "more." :

Quite recently it has been shown that the urea nitrogen in the blood is probably more important than the total nonprotein nitrogen. Normally 10 to 22 mg. of urea nitrogen is present in 100 c.c. of blood. Normally, 60 to 70 per cent. of the total nitrogen is urea nitrogen. Tileston and Comfort, in their important contribution, reported that 100 mg. or more of nonprotein nitrogen per 100 c.c. of blood indicated impending uremia. In their series this was true with two exceptions, one a case of intestinal obstruction, another a severe anemia. One of their eight cases of uremia failed to show marked increase in the nonprotein nitrogen. Foster reports a case of chronic parenchymatic nephritis with uremia with 39 mg. of nonprotein nitrogen and a chronic interstitial nephritis with 120 mg. and no uremia. In passive congestion of the kidney the phthalein test often gives very low readings, while the nonprotein nitrogen test, except in severe cases, shows less disturbance from the normal. Tileston and Comfort and others have shown that by restriction of protein food in nephritis the nonprotein nitrogen in the blood can be reduced. It is interesting to note, however, that fluctuations in blood nitrogen have little, if any, effect on blood pressure, and evidently the hypertension is not due to retained urea. The determination of the nonprotein nitrogen in the blood has given us an accurate index of the ability of the kidney to eliminate nitrogen and the degree of accumulation in the blood that has occurred. The phthalein test shows the functioning capacity of the kidney

only during the two or three hours of the test, the nonprotein nitrogen determination the accumulated incapacity of the kidney.

The renal test diet promises to develop into one of the most important methods of studying renal function, as it is intended to show how the kidney will behave under slight strain. The test is for water, nitrogen and chlorid elimination and the test as shown by Mesenthal may be greatly simplified and still retain much of its value. For a full description of the method see *Archives of Internal Medicine*, 1915, xvi, 733—the phthalein test. The blood used and the renal test meal are with our present knowledge the most important functional kidney tests.

30. Line 40 *add* after “overestimated.”:

Schneider, in a recent investigation, reports that when at rest, in high altitudes, blood pressure is lower than at the sea level, but on exertion the quickening of the pulse and increase in blood pressure are more marked and prolonged than at lower levels.

35. Line 41 *add* after “normal.”:

O'Hare has shown that as a rule salt and water elimination is disturbed earlier than nitrogen excretion.

38. Line 28 *add* after “-tion.”:

Inasmuch as the percentage of urea in the perspiration is considerably higher than in the blood (Plaggemeyer and Marshall) there can be little danger of exciting acute uremia by sweating.

40. Line 16 *read*:

various food principles are the same, **although Mesenthal has shown that in nephritis excessive protein catabolism may occur.** There is no ground for believing

42. Line 37 *add* after “gms.”:

Where opportunity is offered for determining blood urea, the protein restrictions for the patient can be accurately determined and as a result of this work it has been clearly shown that marked restriction of protein, in many cases, is not necessary.

43. Line 31 *add* after “diet.”:

It has been demonstrated that in nephritis the giving of large amounts of protein may increase the blood urea. This is without effect on blood pressure. In other words, the blood pressure is not apparently dependent upon nitrogen retention.

45. Line 4 *read*:

of albumin **and an excessive amount of sodium chlorid.**

47. Line 25 *read*:

recently been introduced by Müller **but apparently does not possess any advantage over the nitrites.**

49. Line 27 (B. F.) Line 28 (F.) *add* after "given.":
Smillie has shown that in nephritis sodium salts are preferable to potassium.

50. Line 2 (B. F.) Line 3 (F.) *add* after "tubule.":
Christian and others have shown that apparently in acute experimental nephritis theocin is injurious to the kidney. However, it may be tried out carefully; in case it excites marked diuresis it may be continued, but if without result it should of course be discontinued. Farr and Walker have shown that theocin, while increasing the water and salt output, does not increase the nitrogen excretion. In some patients with chronic nephritis and edema of renal origin theocin may excite marked diuresis as in a patient of the author's who lost 21 pounds in weight in six days.

51. Lines 1-7 (B. F.) Lines 1-8 (F.) *read*:
cutaneously to animals, excites marked diuresis. **Later results, however, have shown that in man extracts of the posterior lobe, as pituitrin, lessen rather than increase the urinary output.**

There is no evidence that the diuretics mentioned, **except possibly the caffeine group**, are harmful. The

54. Line 38 *read*:
with renal diseases **has usually been considered of cardiac origin, but recently it has been shown that increased carbon dioxid tension due to the acidosis may also be a factor. With this in mind the alkalis may be used freely, as sodium bicarbonate 5-10 gms. (75 to 150 grs.) daily. Rarely is there a real**

59. Line 2 (B. F.) Line 4 (F.) *read*:
and were contraindicated in acute nephritis, **but conclusive evidence that this is true when given in the ordinary therapeutic doses is still lacking.**

Line 30 (B. F.) *read*:
acidity of the urine. **When possible the acidity of the urine should be determined and an alkali like bicarbonate of soda given in sufficient quantities to bring the urine close to the neutral point; where this cannot be done the patient may be given daily 2-8 grains ($\frac{1}{2}$ -2 oz.) of sodium bicarbonate.**

62. Line 9 *add* after "diet.":
Good results may often be obtained by the Karell cure, which consists in a marked restriction of both salt and liquids. For several days the patient receives 200 c.c. of milk at 8 A. M., 12 noon, 4 and 8 P. M., nothing else. After 3 or 4 days dry foods without salt may be added, but the liquids for a period of 3 to 4 weeks are restricted to 800 c.c. daily. Often during the first few days of the cure large amounts of sodium chlorid are eliminated and the beneficial results are due to the low salt and fluid ingestion.

63. Line 6 *read*:

of the chronic interstitial type. It is most frequently of cardiac origin, although increased carbon dioxid tension due to the acidosis probably also plays a role, so the free use of alkalies, as bicarbonate of soda, may be of value.

64. Line 6 *read*:

three times daily, may be used if the blood coagulability is disturbed or still more valuable fresh blood serum 25 to 50 c.c. subcutaneously. For this purpose nothing is more satisfactory than fresh or citrated human blood.

73. Line 30 *add* after "inhalations.":

MERCURIAL NEPHRITIS

During the past four or five years there has been a very marked increase in the frequency of bichlorid poisoning. This has been largely due to the publicity given by the newspapers to cases of accidental poisoning. To those with suicidal intentions these articles gave the necessary information. The ease with which bichlorid could be obtained also furthered their object. Fifty per cent. of the reported bichlorid poisonings, with suicidal intent, in the city of New York during the past 22 years have occurred during the past three years.

Usually within four days after the poison has been taken the patient develops marked symptoms of renal involvement. Lambert and Patterson, who have reported a series of cases, find that the mercury is regularly found in the stomach for several days after being taken. This is not due to retention of the drug but to secretion into the stomach in the effort to eliminate it from the body. For this reason active treatment should be continued for several days or until chemical tests show the absence of bichlorid in the stomach contents, feces and urine. The following treatment has been outlined by Lambert and Patterson. In early cases the patients should be given the whites of several eggs. The stomach is then washed out thoroughly. The later treatment consists in washing out the stomach twice daily for 1 to 3 weeks or until tests show the absence of bichlorid. During the same period of time the colon is irrigated twice daily and the patient receives during the day 8 ounces of milk every two hours and every alternate hour 8 ounces of a mixture containing potassium citrate 1 dram; sugar 1 dram; lactose $\frac{1}{2}$ ounce; lemon juice 1 ounce; water 16 ounces. Day and night during this period the patient is given by the drop method of rectal irrigation a solution containing 1 dram of potassium acetate to one pint of water, and it is important that this be continued day and night until on two successive days the urine has been free from mercury, or in case the test is not made, for a week in moderate cases and two weeks or more in severe poisoning.

74. *Add* under "References.":

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- Goodman, C. Use of Karell Cure in the Treatment of Cardiac and Renal Disease, *Arch. Int. Med.*, 1916, XVII, 809.

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- Schneider. Effect of Altitude on Blood Pressure, *Am. Jour. Physiol.*, 1916, XL, 330.

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- Foster, N. B. Uremia, *Arch. Int. Med.*, 1915, XV, 356.
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- Palmer, W. W., and Hendersen, L. J. A Study of the Several Factors of Acid Excretions in Nephritis, *Arch. Int. Med.*, 1915, XVI, 104.
- Peabody. The Acidosis of Chronic Nephritis, *Arch. Int. Med.*, 1915, XVI, 955.
- Reiss, E. *Tur. Klinik und Einteilung der Urämie*, *Teit f. klin. med.*, 1914, LXXX, 97.

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- McLean, F. C. Numerical Laws Governing the Rate of Excretion of Urea and Chlorid in Man, *Jour. Exp. Med.*, 1915, XXII, 366.
- Mesenthal. Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen and the Specific Gravity of the Urine, *Arch. Int. Med.*, 1915, XVI, 733.
- Tileston, W., and Comfort, C. W. The Total Nonprotein Nitrogen and the Urea of the Blood in Health and Disease, etc., *Arch. Int. Med.*, 1914, XIV, 621.

DIET IN NEPHRITIS

- Blatherwick, N. R. The Specific Rôle of Foods in Relation to the Composition of the Urine, *Arch. Int. Med.*, 1914, XIV, 409.
- Christian, H. C. The Effect of Theobromin Salicylate in Acute Experimental Nephritis, *Arch. Int. Med.*, 1914, XIV, 327.
- Frethlingham, C., and Smullen, W. G. A Study of Different Nitrogenous Diets in Nephritis, *Arch. Int. Med.*, 1915, XVI, 204.
- Smillie, W. G. Potassium Poisoning in Nephritis, *Arch. Int. Med.*, 1915, XVI, 330.

DIURETICS

- MacNeder, W. D. A Study of the Action of Various Diuretics in Uranium Nephritis, *Journ. Pharm. and Exp. Therapeutics*, 1912, III, 423.

SWEATS IN NEPHRITIS

- Austin and Miller. Influence of Sweat Baths on Nonprotein Nitrogen in the Blood, *Jour. Am. Med. Ass.*, 1914, LXXX, 944.
- Plaggemeyer, H. W., and Marshall, E. K. A Comparison of the Excretory Power of the Skin with That of the Kidney through a Study of Human Sweat, *Arch. Int. Med.*, 1914, XIII, 159.

MERCURIC CHLORID POISONING

- Foster, N. B. Mercury Nephritis, *Arch. Int. Med.*, 1915, XV, 754.
- Lambert, S. Poisoning of Mercuric Chlorid and Its Treatment, *Arch. Int. Med.*, 1915, XVI, 805.
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CHAPTER IV

PYELITIS

FRANK SHERMAN MEARA

84. Line 16 *read*:

coccus, **gonococcus**, bacillus typhosus or paratyphoid bacillus, may be the cause.

Line 21 *add* after "read.":

Females are much more commonly affected than males.

Line 22 *read*:

The routes of invasion of pathogenic organisms are **four**: (1) by

Lines 27-28 *read*:

(3) **from bladder to kidney by way of the lymphatics of the ureter, of the pelvis and of the kidney substance, the lymphogenous**; (4) direct transmission from the colon to the kidney, by the lymphatics.

85. Line 29 *add* after "considered.":

Colon bacillus infection occurs frequently during pregnancy, and Wildbolz notes this infection in newly married women and has termed it "defloration pyelitis." The condition is not uncommon after operative procedure, especially about the appendix.

Line 41 *add* after "disturbance.":

Tenderness in the costovertebral angle is the most constant and characteristic sign.

88. Line 19 *add* after "forbids.":

When in an acute or chronic process the parenchyma of both kidneys is involved, their functional integrity should be determined by such tests as the phenolsulphonephthalein of Rountree and Geraghty and the determination of retained metabolites in the blood, such as urea-nitrogen and creatinin-nitrogen, and the diet regulated accordingly, as in acute nephritis. If the parenchyma of one kidney alone is involved as determined by elimination of phthalein and metabolites, on ureteral catheterization, it is still desirable to economize in proteid and salt in the diet.

90. Line 30 *read*:

pirin, **acetylsalicylic acid**, in doses of gr. x to gr. xx (gm. 0.6-1.3) or more every four hours;

91. Line 19 *add* after "so.":

My impression is that in the severe forms of bacillus coli infection in adults, I have had better success with alkalies than with urotropin.

Line 22 *add* after "solution.":

MacGowan advocates lavage of the pelvis with much weaker silver nitrate solutions, 1:20,000 to 1:10,000, which appeals to me as preferable to the stronger solution in acute processes.

Line 41 *add* after "-culosis.":

Since that time numerous reports have been made on vaccine therapy, especially in the colon bacillus cases, with no unanimity of opinion as to its value; but, on the whole, I think the statistics are encouraging.

92. Line 26 *add* after "more.":

The best intervals are about four days.

Line 35 *add* after "treatise.":

Before operation is undertaken an earnest effort to determine the nature of the infecting organism should be made by testing cultures of the urine, taken from either ureter blood cultures, or cultures from probable sites of primary infection. If bacillus coli is determined, the case is in quite another category from those due to such pyogenic organisms as streptococci pyogenes and staphylococci, for the tendency of the latter is to abscess formation, of the former to diffuse inflammation.

Clinically, the one striking difference in these two groups is the absence of profound toxemia and prostration in the colon group, though chills may initiate the attack, the fever run high, and local signs be acute.

In the colon cases a surgeon is loath to operate, unless progressive toxemia occurs or the case be exceptionally fulminating in character, and then he is prepared to be more conservative and prefer decapsulation, incision and drainage of infected areas to an immediate nephrectomy.

Line 36 *read*:

In the pyogenic cases, if an uncomplicated perinephritic abscess exists, incision and drain-

93. Line 19 *read*:

methods recently by Rowntree and Geraghty **and more recently by George Gilbert Smith and others.**

95. *Add* under "References.":

MacGowan. Jour. A. M. A., Jan. 16, 1915.

Smith. Separate Renal Function, Jour. A. M. A., Jan. 16, 1915.

Wildholz. Quoted from Kretschener, Colon Bacillus Pyelitis, Int. Med. Jour., Feb., 1915.

CHAPTER V

HYDRONEPHROSIS

FRANK SHERMAN MEARA

96. Lines 8-9 *read*:

A movable kidney, **especially if the upper portion of the ureter is fixed**, by causing a kinking of the ureter, is another potent cause. **It must be remembered, too, that infection of the pelvis or ureter, without other cause for stenosis, may be responsible for hydronephrosis.** Pelvic tumors, inflammation, and movable kidney make

Line 32 *add* after "uremia.":

Although their theories have not been universally accepted the observation that the opposite kidney may be affected has been frequently made and constitutes a potent reason for operative interference.

97. Line 3 *add* after "septicemia.":

[C. Fenger noted the abnormal arrangement of renal arteries as one of the causes of hydronephrosis. Mayo, Braasch and MacCarty found an anomalous arrangement of renal vessels at the point of ureteral obstruction in 20 of 27 cases of hydronephrosis.—EDITORS.]

Line 8 *add* after "urine.":

Braasch believes this type to have an anatomical basis, due to congenital conditions and finds the average at onset of symptoms to be 21 years.

Line 20 *add* after "change.":

A tumor is by no means constant and much damage may be done to the kidney before collections sufficient to afford a palpable tumor occur. Cabot has made a strong plea for early diagnosis, recalling that the symptomatology may be that of renal colic or pyelitis, even when no stone is present or the urine with pus and blood, suggesting infection, is sterile.

Pyelography helps greatly in the appreciation of these cases and operation is early indicated, before irreparable injury to the kidney parenchyma ensues.

98. Line 1 *read*:

plates should be secured to detect a possible stone, **the distention determined by pyelographic methods on the overdistention method of Kelly, and thorough abdomi-**

99. *Add* under "References.":

- Beer. Experimental Study of the Effects of Ureteral Obstruction on Kidney Function and Structure, *Am. Jour. Med. Sci.*, June, 1912.
- Braasch. The Clinical Diagnosis of Hydronephrosis, *Int. Med. Jour.*, Nov., 1914.
- Cabot. The Diagnosis and Indications for Operation in Early Hydronephrosis, *Jour. Am. Med. Ass.*, Jan. 4, 1913.
- Mayo, Braasch and MacCarty. *Jour. Am. Med. Ass.*, 1901, lii, 1383.

CHAPTER VI

NEPHROLITHIASIS

FRANK SHERMAN MEARA

108. Line 40 *add* after "primary.":

Kahn and Rosenbloom find that the vast majority of renal calculi are composed of oxalate of lime and, though uric acid and urates are found in nearly all, it is the oxalates that compose the main portion.

110. Line 4 *add* after "-tion.":

If, as the analyses of Kahn and Rosenbloom would seem to show, oxalate of calcium plays so large a rôle and uric acid and its salts so small a one in the formation of renal calculi, their contention that alkalies are contraindicated and advice to render the urine acid would seem logical.

One would use benzoates or salicylates for such a purpose in doses sufficient to effect the desired result.

Line 22 *add* after "obstruction.":

The presence of a calculus should not precipitate a surgical procedure unless there are evidences at the time of its discovery of damage or, by virtue of its size, site, etc., a threat of damage to the kidney; for a stone in the pelvis may lie long quiescent or a stone in the pelvis or ureter may be passed without trouble or danger; but any calculus is rife with danger and the patient entertaining it should have adequate examination from time to time to early appreciate renal changes, infection and local injury. Moreover, the mere act of ureteral catheterization may so dislodge a stone from its point of impaction as to facilitate its passage.

Line 27 *add* after "attempted.":

Buerger has reported a fair measure of success with the latter method.

Among other measures that have met each with its modicum of success are cutting the meatus of the ureter to make more room, using a special ureteral forceps and even fulguring.

111. Line 7 *read*:

his ability by the use of the functional tests, **determination of urea—or total nonprotein nitrogen in the blood**, study of water, saline and

Add under "References.":

Kahn. Arch. Int. Med., Jan., 1913.

—— and Rosenbloom. Jour. Am. Med. Ass., Dec. 31, 1912.

Rosenbloom. Jour. Am. Med. Ass., Oct. 9, 1913.

CHAPTER VII

TUBERCULOSUS KIDNEY

FRANK SHERMAN MEARA

113. Line 41 *add* after "tuberculosis.":

Laurason Brown says "that when a patient with tuberculosis develops albuminuria, renal tuberculosis should be thought of at once."

114. Line 1 *read*:

examination, is almost invariably found. **If the organism is not found the sediment should be injected into a guinea pig.** The red bloods cells are almost

Line 5 *read*:

the diagnosis of tuberculosis in the patient as certain and in the kidney as highly probable, still it is possible for the kidney to excrete the bacilli without itself becoming involved; moreover, tuberculosis of epididymis, spermatic cord, prostate or seminal vesicles may be the cause of the bacilluria; hence, a detailed examination of this tract is indicated. To localize the lesion a cystoscopy is imperative.

116. Line 24 *add* after "more.":

In a damaged kidney, however, since economy in proteid may be advantageously exercised, 60 to 80 grams will probably be quite sufficient.

117. Lines 13-14 *read*:

doses, better yet, human serum in amounts of 10, 20, 50 c.c. or even whole blood into the subcutaneous tissue in 10 to 30 c.c. doses, gelatin foods by mouth to meet theoretical considerations dealing with enhanced coagulation. **In a very severe hemorrhage a transfusion might be indicated.**

118. *Add* under "References.":

Brown. The Significance of Tubercle Bacilli in the Urine, Jour. Am. Med. Assn., March 13, 1915.

II. DISEASES OF THE BLADDER

CHAPTER I

CYSTITIS

E. L. KEYES, JR.

121. Line 23 *read*:

As a last resort **anastomosis of the ureter and colon** has been resorted to to relieve the

122. Line 21 *add* after "latterly.":

Thyroid extract has been used successfully.

IV. DISEASES OF THE NERVOUS SYSTEM

CHAPTER I

DISEASES OF THE SPINAL CORD

JOSEPH COLLINS AND EDWIN G. ZABRISKIE

194. Lines 7-31 *substitute:*

The selection of the remedy has been greatly modified by the addition of Ehrlich's salvarsan to our pharmacal armamentarium. Its power as a therapeutic agent can no longer be questioned and it is our belief that its value is far greater than mercury in the treatment of all syphilitic diseases of the nervous system, including tabes. Its administration may be either intravenous or intraspinous. If the former is selected it is introduced into the median basilic vein in doses of 0.2, 0.3 or 0.6 gram. If care be taken not to injure the vein, rigid surgical cleanliness adhered to, freshly distilled water be used and the proper neutralization of the substances be obtained, little or no discomfort should follow its administration. Full doses, i.e., 0.6 gram, should be given once in 10 days or a fortnight; the so-called intensive methods consist in the administration of small doses, that is, 0.2 or 0.4 gram every fifth day for ten to fifteen doses, or 0.1, 0.2 or 0.3 gram every day for three or four doses, then an interval of two days, another series of four and so on until relief is secured. They have been recommended for cases of obstinate crises or severe lancinating pains. The intraspinous method consists in the direct introduction of inactivated human serum, salvarsanized either *in vitro* or during its preparation, into the subarachnoid space by lumbar puncture. It is based on the well known facts that experimentally the choroid is relatively impermeable to organic substances, and that arsenic is rarely recovered from the fluid after intravenous administration. The advantages claimed for the intraspinous method are: the serum is spirocheticidal, it may contain antibodies, the local irritation of the meninges may increase their permeability, assist in the resolution of exudates, or have the beneficial effects of artificial hyperemia; furthermore, the successful results obtained where other methods have failed amply justify it.

There have been several vigorous protests against this method on the ground that it is an exceedingly dangerous procedure and liable to cause grave accidents.

Our own feeling in the matter is that the method is of great value in specially selected cases, and that whereas it is difficult to administer and always causes more or less root pain and is somewhat dangerous, it should be used where the intravenous methods have failed. It should never be employed indiscriminately or as routine practice, as there have been deaths, acute softening, and meningomyelitis ascribed to its use and one should never forget the possibility of infection. The cases best suited to its use are the exudative meningeal types with a high cell count and globulin excess, or else the obstinate cases of lancinating pains, gastric or other crises, and severe headaches. Ravaut's method of injecting salvarsan dissolved in salt solution has been abandoned in this country because of the many unfortunate results. Byrne has advocated a serum containing bichlorid of mercury, but thus far our experience is too limited to form a proper opinion of its value.

234. Line 8 *add* after "rare.":

The cause of poliomyelitis has been thought to be a minute, nonfilterable virus, which can be grown in special culture media and recovered from inoculated animals. It has been carried along for twenty generations, and there seems little doubt that among the different cultures investigated only a few are really pathogenic. The chief difficulties which prevent a more thorough knowledge of all its properties lie in the fact that, for practical purposes, it can only be cultivated in monkeys. These animals are highly resistant to the organism, and therefore the virulence of the various strains and their power of persisting through generations cannot be standardized. In a recent publication it has been shown that the organism can live for a year in culture media and produce the disease after several inoculations. According to Flexner and his followers, the principal, if not exclusive, avenue of entry is the nasal mucosa and its lymph channels, and infection results by means of direct contact with the dried or moist nasal discharges of a carrier. This may occur through accidental contact of the hands with the clothing, etc., of a carrier through coughing, expectorating, etc. Early experiments by Rosenau, Anderson and Frost suggested that the stable fly could carry the disease, but more recently the same authors and others abroad failed to corroborate this. There is no doubt, however, that the chief carrier is man, since the virus has been obtained not only from the nasopharyngeal secretion and rectal mucus of convalescents at periods varying from a few weeks to several months after recovery, but it has also been found in the nasal secretion of perfectly healthy individuals.

[Mathers (*Jour. Amer. Med. Assoc.*, Sept. 30, 1916) reports the find-

ing of a gram positive micrococcus in the brain and cord of 7 out of 8 cases of poliomyelitis. "The organism is of low virulence for rabbits, but when injected intravenously in large doses, lesions of the central nervous system are produced with paralysis which may resemble that of infantile paralysis, especially as it affects the extremities." Whether this organism is a secondary invader, or whether it represents one stage of a pleomorphic organism which is the cause of the disease, or whether the real virus in the animal experiments was introduced along with the micrococcus can only be determined by further study. Rosenow (*Jour. Amer. Med. Assoc.*, Oct. 21, 1916) and Nuzum and Herzog (*ibid.*, Oct. 21, 1916) report the finding of similar organisms in cases of poliomyelitis and likewise the production of paralysis in animals by the injection of cultures.—EDITORS.]

237. Line 30 *add* after "winners.":

The Health Department of New York considers the period of incubation to be from five to nine days, and quarantines the family for about two weeks (1916).

Line 41 *add* after "fluid.":

Urotropin and quinin are used extensively as prophylactic measures. Urotropin is given for the same reason that it is administered so freely after operation, especially as formaldehyd is thought to be present in the spinal fluid after its ingestion. Quinin is given because of its well-known power to produce leukocytosis and even increase the cells in the fluid. There are, however, as yet no very convincing data of the efficacy of these two drugs. Lumbar puncture should be done in practically every case where there are no focal contraindications. The withdrawal of fluid relieves pressure from congestion and thus alleviates the suffering from pain and tenderness. If the lesion is in the medulla it should only be resorted to after careful consideration, since the sudden relief of pressure in this region may lead to grave consequences. Meltzer has recently advocated the intraspinous administration of adrenalin in two to five minim doses. The results thus far are contradictory and do not promise much success. The intraspinous administration of serum from individuals who have recovered from the disease has been recently employed, but sufficient data are not yet at hand to warrant a conclusion as to the efficacy of this method of treatment.

CHAPTER II

DISEASES OF THE PERIPHERAL NERVES

HOWELL T. PERSHING

283. Line 8 *read*:

sutured should be enveloped if possible in a sheath of fascia, **or other suitable animal membrane**, to protect it

Line 37 *add* after "agencies.":

If this condition, as now seems probable, is really due to recurrent infection, the most important indication is to find and remove the source of infection, which may be in the tonsils, teeth, ear, accessory sinuses or any part of the body where pus is formed and not freely drained.

286. Line 35 *read*:

administration. **Sodium veronal** and the solution of veronal known as neuronidia have the advantage

292. Line 23 *add* after "(Oppenheim, 30).":

After an injury or operation in the neighborhood of the plexus or a nerve trunk, e.g., the removal of glands from the axilla, neuritis may occur as a remote consequence from late changes in the wound.

Line 28 *read*:

fascia **or other suitable membrane**. The ulnar nerve is sometimes dislocated from its position back of

293. Line 25 *read*:

salicylates **and removal of all sources of infection** in rheumatism, diet in diabetes. Analgesics, counterirritation,

296. Line 2 *read*:

needle, such as is used for lumbar puncture, **or an ordinary one 2½ inches long**, is inserted in the median

Line 19 *read*:

of its varying causation. **I have secured valuable temporary relief from them but no permanent result.** If these injections fail **Levy and Baudouin** recommend sub-

298. Line 2 read:

may call for treatment. If the joint is thought to be in a rheumatic condition careful search for a removal of the source of infection is the most important indication; meanwhile a salicylate should be given. Injections into the nerve trunk are not indi-

Line 35 read:

Any streptococcus infection, puerperal fever, typhoid, influenza, even gonorrhea, may be such a cause.

299. Line 13 read:

angles to the leg, **by a pillow or, if necessary**, by a large sand bag or a board placed across the bed,

301. Line 8 read:

strongly hypertonic, others isotonic salt solutions, **but only the isotonic solution should be used. In one case a strong solution caused permanent paralysis.** Some add beta-eucain, **novocain**

Line 11 read:

better than, salt solutions. The following will serve every purpose: **novocain**

303. Line 31 add after "pain,":

in the peroneal or posterior tibial distribution according to the seat of the greatest spontaneous pain. The sciatic at this point is really two nerves in one sheath, the fibers coming from the lumbar cord and going to the peroneal nerve lying on the outer side, while those coming from the sacral roots and going to the posterior tibial nerve are on the inner side.

Line 39 read:

tions. **If very severe, as it sometimes is, it must be controlled with morphia.** In approximately two-thirds of the cases treated by this method

Line 42 read:

method is as safe as any direct action on a large nerve can be, **but there is some risk involved in it. A**

304. Line 1 read:

pletely, as the solution, **properly prepared and sterilized, has no harmful chemical effect. If the site of injection should become infected it would be a very serious complication. With due care this is exceedingly improbable, but it is possible even with a perfect technique if the patient has a focus of suppuration elsewhere in the body, the originally sterile site of injection becoming the place of least resistance to a metastatic infection.** For further de-

CHAPTER III

DISEASES OF THE CRANIAL NERVES

HOWELL T. PERSHING

305. Line 15 *read*:

Salvarsan is **at first** contraindicated, **but may be used later with great advantage**. If this **treatment** fails, or it is certain that the growth

306. Lines 23-26 *read*:

cases of inflammation of the upper part of the spinal cord is not **definitely known, but we may infer that it is a metastatic infection either from the focus in the spinal cord or from its primary source elsewhere in the body**. Unfortunately, the **myelitis** is scarcely amenable to treatment of any kind, and tends rapidly toward a fatal issue, **but an effort should be made to find and remove the primary focus**.

Line 41 *read*:

cause appears, the case is hopeful, **and the search for a source of infection should be continued**.

307. Line 26 *read*:

As in optic neuritis, salvarsan is contraindicated **until mercury and iodid have been used**. The possibility of lead

308. Line 10 *read*:

lead to the more general diagnosis and the appropriate treatment. **Fracture of the skull with consequent pressure from hemorrhage may be a cause and the nerve may completely recover when the blood is absorbed**. Vari-

309. Line 23 *read*:

symptoms of organic intracranial disease, either vascular or degenerative, **and the paralysis may become permanent**.

311. Line 14 *add* after "foramen.":

Removal of any remaining source of infection is the paramount indication.

Line 15 *read*:

Rheumatic and Idiopathic Cases.—These should always be regarded as possibly infectious and thorough search should be made for a pri-

mary focus with a view to its prompt removal. The rheumatic cases if seen early

Line 20 *read*:

tage in such cases of being a salicylate, **thus probably antagonizing streptococcus infections and** favoring the prompt elimination

318. Line 15 *add* after "punctures.":

In one of my cases of very severe labyrinthine vertigo which had resisted all other treatment there was very marked relief for a year following a single puncture. About 15 c.c. should be withdrawn and the patient should remain in bed for two days.

322. Lines 26-27 *read*:

as the cause is not **entirely** known, **but** it is symptomatically a form of multiple neuritis, **and is caused by an inefficient diet.**

325. Line 16 *read*:

multiple neuritis is given in special articles. **The great thing is to recognize infection as the cause and to find and remove the primary source.** The occurrence of neuritis calls

CHAPTER IV
THE NEURALGIAS
HOWELL T. PERSHING

335. *Add* after heading "TREATMENT AS TO CAUSE":

Writing of the causes of neuralgia now must show a lack of precision just as it did to write on the causes of acute articular rheumatism before anything definite was known of the streptococcus as the infecting agent or of the tonsils and other organs as points of invasion. A definite and constant cause of neuralgia not being known, we are obliged to consider a large number of possible causes without being sure of the relative importance of any. It is clear that the sensory neuroses involved are so changed that a very slight stimulus from the periphery excites violent pain, and it also seems clear that this change is in the peripheral neurons whose bodies are in the gasserian ganglion or in the posterior root ganglia. What causes the irritability we do not definitely know, but I believe it will prove to be an infection.

Our most valuable means of treatment, injection of alcohol, merely blocks the sensory currents from the periphery, thus shielding the ganglion from disturbance, but also sacrificing the normal function of the nerve. What we ought to be able to do is to reduce the excessive irritability of the neurons so that they would respond normally to ordinary stimuli; and this can be done only by removing the cause. Until the cause is known we must try to remove all possible ones.

Line 19 *read*:
and middle ear **and of the tonsils** should be investigated. But it is defect of the teeth that

Line 22 *read*:
ray **films** if there is any question of faulty eruption **or suppuration at the roots**. The physician must

356. Line 5 *read*:

glasses at short intervals. Local irritations **or sources of infection** in the viscera of the chest,

Lines 43-44 *read*:

ently caused by exposure to cold **with rheumatic infection**, warmth, both local and general, is indicated, together with mod-

337. Lines 24-26 *read*:

Specific Infections.—Influenza is the most important of the acute infectious **fevers**. It should be treated like the acute rheumatic form, **but with extra care to secure** the most absolute rest possible and to prevent a relapse, which

Line 44 *read*:

Mental Condition.—The emotional condition of the patient is important. Grief, anger,

338. Line 9 *read*:

Climate.—Many neuralgic patients are plainly influenced by climate, season and

343. Line 37 *add* after "it.": (B. F.)

After piercing the skin the needle is to be moved slightly to one side or the other of the line and the characteristic numb pain on the side of the nose will tell when the injection is being made at the right point.

345. Line 19 (B. F.) 346. Line 10 (F.) *read*:

should be entered from the outside, **half an inch back of the second lower bicuspid**, pointing obliquely downward and a

350. Line 16 (B. F.) Line 39 (F.) *add* after "sterilized.":

The site of injection, though sterile at first, might possibly be secondarily injected from a focus of suppuration elsewhere in the patient's body.

355. Line 5 (B. F.) 356. Line 2 (F.) *read*:

local cause to be removed **and the normal function of the nerve should not needlessly be sacrificed**.

Line 14 (B. F.) 356. Line 10 (F.) *read*:

posure to cold and wet **plus a probable subinfection**, and yields readily to general and local

CHAPTER V

DISEASES OF THE BRAIN COVERINGS

JULIUS GRINKER

362. Lines 1-11 *substitute:*

In the treatment of diseases of the nervous system, as perhaps in no other class of human ailments, a correct diagnosis must precede all efforts at definite relief. I have, therefore, introduced each chapter with a brief discussion on pathology, etiology, and diagnosis. My principal aim has been to impress the reader with the importance of taking a broad outlook on the disease and its management, rather than to burden his memory with minute descriptions of the numerous methods of treatment detailed in the literature of the day. In conformity with this thought I have put the greater emphasis not on the latest, but the most useful means of combating the ravages of organic disease of the nervous system.

367. Line 30 *read:*

the surgical treatment are largely taken from Keen, **whose opinions have found general acceptance.**

379. *Add* under "References.":

ACUTE CEREBRAL MENINGITIS

Bing, R. Neuere Arbeiten über Meningealerkrankungen Sammel referat, Med. klin. No. 31, 1912, p. 1228.

Kopetzky. Meningitis, Nature, Cause, Diagnosis. Principles of Surgical Relief. An Experimental and Critical Study. The Laryngoscope, xxii, No. 6, 1912, p. 797.

Morgan, H. J. Meningeal Affections in Infancy and Childhood, Ohio State Med. Jour., June 15, 1912.

TUBERCULOUS MENINGITIS

Hochstetter. Ueber die Heilbarkeit der Tuberkulösen Hirnhautentzündung, Deutsch. med. Wochenschr., No. 12, 1912, p. 554.

- Koch, H. Entstehungsbedingungen der Meningitis Tuberculosa, Zeitschr. f. Kinderheilkunde, Originale, Bd. v, H. 5, 1912, p. 355.
- Rabinovitsch. Tuberculous Meningitis, New York Med. Jour., xevi, No. 6, 1912, p. 280.
- Reichmann, V., und Rauch, F. Zwei geheilte Falle von Meningitis Tuberculosa, Münch. med. Wochenschr., 1913, lx, p. 1430.
- Rhein. Tuberculous Meningitis. A pathologic report of nine cases, Jour. Am. Med. Ass., lix, No. 3, 1912, p. 165.

CHAPTER VIII

ENCEPHALITIS

JULIUS GRINKER

413. Line 40 *add* after "periods.":

When bromids are not well borne, *Luminal* (Bayer or Merck) may be given in daily doses of grains one and one-half to two (0.1 to 0.13 gm.)

Lines 41-42 *read*:

Surgical Treatment.—In infantile cerebral palsy operations on the brain **may be undertaken in selected cases.** **Patients** have been oper-

414. Lines 1-5 *read*:

In my experience the attacks have almost invariably returned. In **some** cases the operation itself was fatal. **With** E. D. Henschen, I now advise operation in cerebral palsy, **but only** when undertaken within the first few months **or years** after the development of epileptic attacks following cerebral palsy. I advise operation, **particularly when** focal signs of some kind are present.

CHAPTER IX
CEREBRAL ABSCESS

JULIUS GRINKER

424. *Add* under "References.":

Dench, E. B. Brain Abscess of Otitic Origin, Based on a Study of Twenty-one Personal Cases, *Annals of Otology*, Sept., 1912.

Dereum, F. X. Diagnosis and Localization of Brain Abscess, *Journ. Am. Med. Assn.*, lix, No. 12, 1912, p. 1097.

CHAPTER XIV

HYDROCEPHALUS

JULIUS GRINKER

469. *Add* under "References.":

Bluhdorn, Kurt. Meningitis Serosa und verwandte Zustände im Kindesalter, Berl. klin. Wochenschr., No. 38, 1912, p. 1796.

CHAPTER XV

SYPHILITIC DISEASES OF THE BRAIN

JULIUS GRINKER

477. Lines 13-19 *read*:

test. **Lange's colloidal gold test has a certain diagnostic value in brain syphilis, though not as great as in general paresis.**

479. Line 9 *read*:

five years, and repeated examination of spinal fluid and blood must have been negative.

Line 26 to **489.** Line 2 (inclusive) *substitute*:

When the diagnosis, syphilis of the brain, is definitely established, energetic antisyphilitic treatment must be instituted without delay. Inaction often spells irreparable damage to the delicate nervous tissues.

While the treatment of nervous syphilis does not differ essentially from that of syphilis in general, yet certain methods have been recently developed which aim to attack the disease locally. After the laboratory and clinical diagnosis of cerebral or cerebrospinal syphilis has been definitely made, it is quite essential to search out the regional peculiarities of the disease before deciding on a plan of action. The treatment should take as its starting point the new clinical division of syphilitic nervous diseases into, (1) *interstitial* types, which include most of the lesions previously classed under cerebrospinal syphilis; (2) *parenchymatous* types, which comprise the group of diseases formerly known as para-, post-, or meta-syphilis, with tabes and general paresis as conspicuous examples; and (3) *vascular* syphilis and its numerous accidents.

The most favorable results from treatment are recorded for the interstitial variety of nervous syphilis, improvement being noted both in the biologic reactions and in the clinical findings. This improvement is best explained by the local peculiarities of the lesions, which consist for the most part of edema and pressure on nerve centers, but not of destruction of the nerve parenchyma. Provided nerve tracts and centers have been

spared the ravages of spirochetal activity, the cures of this variety are occasionally next to perfect. For the same reason, the treatment of parenchymatous syphilis is not nearly as satisfactory,—the beneficial results being limited mostly to the removal of symptoms produced by the inflammatory and exudative processes also present in this variety. Least favorable for therapeutic efforts is the third group, so-called luetic endarteritis, in which the blood and spinal fluid frequently show negative findings, while the patients present the worst examples of thrombotic softening of the brain and spinal cord. Improvement, if it occur at all, is proportionate to the degree in which the endarteritis and its consequences can be influenced.

The drugs at our command in the management of nervous syphilis are, in the order of their importance, mercury, salvarsan or neosalvarsan, and iodids.

Mercury.—This classical remedy, which still is, and probably will remain so for a long time, our most effective weapon in the fight against syphilis, may be administered in various ways: by the mouth, in the form of pills or solutions; by the skin, in the form of inunctions or fumigations; by injection, either intravenously or intramuscularly.

The treatment by means of the well known "little pills" belongs to the past. Nothing was ever more delusive and disastrous of results in a negative way than the fond hope that a patient was being treated when he was only playing with treatment. To this so-called treatment may be charged the development of many cases of tabes and paresis, which parenchymatous diseases of the nervous system were permitted to germinate and reach full growth while the patient was supposedly under his physician's care. For reasons that are obvious, progressive physicians everywhere have discarded the routine administration of mercury by mouth. There are but very few occasions left in which this form of mercurialization may still be recommended.

The most effective and most readily applied form of mercurial therapy is by inunction. The inunction method consists in rubbing into the patient's skin a varying amount of mercurial ointment,—an average dose being considered one to two drams (4-8 gm.). This quantity is placed in a waxed paper and the patient is directed to rub its contents into the body, selecting a different part for each subsequent rubbing. After twenty minutes to one-half hour's rubbing the ointment will probably have disappeared and a piece of flannel bandage may then be tied around the part, which is to remain there during the night. The parts chosen for this purpose are the flexor surfaces,—groins, bends of elbows, the popliteal spaces, and the inner surface of the thighs. To facilitate absorption of the ointment, the skin is made more supple by the taking of a lukewarm bath before each rub and of a full hot bath every fourth night. Thirty rubs constitutes a course of treatment. Between each mercury course a

period of iodid administration is interposed. The iodid of potassium or sodium is prescribed in doses, beginning with 30 drops of the saturated solution, gradually increased to one dram (4 gm.), three times daily after meals, taken in liberal quantities of milk or water. Having taken iodids for a period of four weeks, the mercurial rubs are again resumed and another course of treatment is finished. The iodids are again administered and alternated with courses of mercury. These regular alternations may be persevered in during the entire period of active treatment, or the so-called "mixed" treatment may be substituted. The latter consists in the simultaneous exhibition of mercury and iodids during a period of six weeks, followed by complete cessation of treatment for another six weeks. During this interval the patient is ordered to take a generous and unrestricted diet, tonics and rest. At the expiration of this resting period treatment is again resumed and another rest is followed by treatment. This is carried through alternately with periods of rest during one to two years, depending on how rapidly the Wassermann test in both blood and spinal fluid can be made and kept negative.

A good substitute for the ordinary mercurial ointment, which is unsightly and apt to "tell a story," has been found in oleate of mercury, which is comparatively cleanly and produces results as rapidly as other preparations of mercury applied to the skin. A dram (4 gm.) of the ten per cent. oleate of mercury is used night and morning for four days. Thereafter the same dose is continued only once daily for four days more. If no evidence of salivation has appeared, the double dose may be resumed; otherwise we return to the single dose. The oleate is rubbed into the skin by means of a piece of flannel which may be used continuously, selecting for each application a different portion of the body. While irritation to the skin may also occur from the oleate it has the advantage of permitting absorption to take place more readily from all parts of the body than is possible with the blue ointment. A course of treatment lasts six weeks, the same as with unguentum hydrargyrum. Rubbings may be alternated with the iodids, or both may be ordered conjointly.

MERCURIAL INJECTIONS.—The treatment by injections of mercury is intended to deliver a more concentrated and energetic blow to the spirochetes. The choice of the mercurial salt, whether soluble or insoluble, is merely a matter of convenience; whereas the soluble salts must be injected daily or at least every other day, the insoluble mercurials need not be injected oftener than once or twice weekly. Though well known on the continent of Europe, the injection of mercury is comparatively new with us. Of all forms of mercurial administration this should be the method of choice in all serious nerve lesions of syphilis, for by no other route, save perhaps the intravenous, can mercury be forced more rapidly into the general circulation. In those instances injections may

be administered daily or even twice daily of the soluble salts, biweekly of the insoluble ones. In fulminant types of nervous syphilis, and when the disease has assumed widespread proportions, we may advantageously flood the system with the soluble salts of mercury.

Injection therapy, which is practically always given intramuscularly, requires that certain precautions be observed. Regardless of which preparation is being used, careful asepsis must be maintained with reference to needle and syringe, patient's skin, and physician's hands. Blood vessels should not be perforated and piercing of nerve trunks is to be avoided. The buttocks have become the favorite site for intramuscular injections. The exact spot of preference is the center of a line drawn from the anterior superior spine of the ilium to the upper end of the intergluteal fold,—this point being well above and to the outer side of important vessels and nerves emerging from the pelvis through the great sacrosciatic foramen. The most commonly used soluble mercurials are the bichlorid, succinamid, and the red iodid of mercury, in doses varying according to the severity of the case, from one-eighth to one-half grain (0.0075-0.03 gm.), injected daily into the buttocks to a depth of about 5 cm. A course of treatment consists of thirty injections, which may be repeated after a longer or shorter interval, depending on how soon the Wassermann test on blood and spinal fluid becomes negative.

Of the insoluble salts of mercury, the most important and most generally useful are the so-called "gray oil" and the salicylate of mercury, either of which is given in doses of approximately one grain (0.06 gm.) once or twice weekly, injected deeply into the buttocks. The insoluble forms of mercury, after being deposited in the muscles, undergo slow absorption and thus continue to feed the body with small doses of mercury. As the rate of absorption is not within our control and varies considerably in different individuals, we examine frequently for signs of beginning salivation. On the first appearance of reddened or spongy gums and of the peculiar mercury breath, injections are discontinued. Indeed, it is a good rule to interrupt the treatment after each series of eight injections, in order to study the possible development of mercury poisoning.

Mercury, irrespective of preparation or method used, requires scrupulous attention to the oral cavity. The teeth and gums should be thoroughly brushed after each meal with powdered chlorate of potash, and the mouth rinsed with a 3-5 per cent. solution of the same substance, or listerine and similar antiseptic mouth-washes may be used. Needless to add that all articles of diet containing even a trace of the mineral or organic acids should be excluded, which means also raw and cooked fruit. Neglect of these precautions is most likely to produce salivation, which necessitates the interruption of treatment.

Salvarsan and Neosalvarsan.—The various methods of administering these powerful spirocheticides being well known, I shall limit myself to a

discussion of their special applicability to the treatment of nervous diseases.

When salvarsan was first given to the profession, we believed that it possessed death-dealing qualities against the spirochetes, provided the attack was directed against their early lesions. Ehrlich himself warned against the use of salvarsan in the very late lesions and especially in diseases of the central nervous system, in which he advised the experimental use of small doses of the remedy cautiously repeated. It appears quite probable that, largely on account of the small doses administered, many of the spirochetes situated in the outlying districts of the nervous system which escaped the destructive action of salvarsan began to multiply at an enormous rate and shortly produced the disagreeable relapses called neurorecidives or neurorecurrences. Many controversies as to the true nature of these unforeseen accidents were carried on, and progress for a time at least was retarded. Fortunately for the advancement of this form of therapy it was found later that additional larger doses of salvarsan administered after the development of these nerve accidents had a tendency to cause the disappearance of the symptoms. At about the same time it had been discovered that salvarsan or neosalvarsan combined with mercury was more effective than when either of these remedies was administered alone. When finally the biologic proof was brought that all forms of this disease are real syphilis, not merely somewhat related to it, hopes were entertained that all syphilis would be treated alike. This was found to be a mistake. Because certain early syphilids yield readily, within a very short time, to one or two injections of salvarsan, is no proof that cerebrospinal syphilis will be cured in the same way. On the contrary, it has been positively demonstrated that the late and deep-seated lesions of syphilis, especially those of the central nervous system, require repeated, fair-sized doses to bring about results. In conformity with this reasoning Collins and others have adopted what they call the "intensive" intravenous method of treating nervous syphilis.

This method aims to flood the system with salvarsan or neosalvarsan intravenously, only two days being allowed between injections, of which five are administered, unless there are contraindications. During the intervening days between injections the patient receives inunctions of mercury, or he is given injections of the salicylate of mercury in one-half to two grain doses (0.03-0.12 gm.), or the mercury bichlorid in doses of one-eighth to one-half grain (0.008-0.03 gm.) is injected intramuscularly every day or every second day. After treatment lasting three or four weeks a laboratory examination of blood and spinal fluid is made, which decides whether treatment is to be continued. Usually the series of injections is repeated after three months. This plan of treatment is consistently adhered to until all evidence of syphilis has disappeared from blood and spinal fluid.

Though the "intensive" treatment had been adopted by many clinicians, and good results were not rare, yet numerous observers felt dissatisfied with the slow progress obtained from this rather heroic treatment. Besides, relapses were as common as under the old line of treatment. Nothing was more natural, therefore, than to conclude that there must exist some anatomical barrier to the free transmission of salvarsan from the general circulation into the central nervous system. And indeed several observers have actually furnished the experimental and clinical proof that little or no salvarsan enters the subarachnoid space. According to Goldman and others, the choroid plexuses, which constitute the great source of the spinal fluid, functionate somewhat like a filter, in that certain poisons, salvarsan and neosalvarsan among them, are not allowed to pass into the ventricular system, while the fluid elements are given free passage. Though this peculiar arrangement serves as a great defensive measure against the entrance of poisons into the nervous system, it also prevents the entrance of needed remedies. It must be considered a triumph for therapeutic resourcefulness, therefore, when Marinesco, Robertson, and particularly Swift and Ellis, who all carried on similar investigations, thought of overcoming this disadvantage by an effort to reinject into the subarachnoid space the patient's own serum previously charged with a full dose of either salvarsan or neosalvarsan. Thanks to the ingenuity of Swift and Ellis, an intraspinal therapy has been worked out which bids fair to revolutionize our entire treatment of nervous syphilis.

Swift and Ellis describe their method substantially as follows: The patient receives an intravenous injection of 0.5 gm. salvarsan, given in the usual manner. One hour after this administration enough blood is withdrawn from the patient's vein to give at least 15 c.c. of serum. The blood, obtained under aseptic precautions, is permitted to coagulate, and is then placed in the ice-chest over night. Next morning the separated serum is very carefully decanted off into a centrifuge tube, and permitted to centrifuge for about half an hour. The clear supernatant fluid is pipetted off from the few red cells at the bottom, and poured into a graduated cylinder up to the 12 c.c. mark, and then brought up to 30 c.c. by the addition of sterile 0.9 per cent. NaCl solution. This is placed in a 56° C. thermostat for thirty minutes, and the mixture of serum and salt is ready for intraspinal injection.

The solution is injected at body temperature. With the patient lying on his side, in bed, near the edge, the back is rendered aseptic in the ordinary manner, and the area to be punctured anesthetized with 2 per cent. sterile novocain solution. The lumbar puncture needle is introduced in the usual manner, and about 30 c.c. of cerebrospinal fluid is withdrawn, or a quantity that will reduce the intraspinal pressure to about 30 or 40 millimeters. This is gauged with a 3-millimeter glass tube graduated in centimeters and millimeters. When the desired pressure is

reached, the connection with the gauge is discontinued. The serum-salt mixture is poured into a Luer syringe (large size) carrying at the delivery point a sterile piece of connecting rubber tubing about 12 inches long. This tubing is then attached to the lumbar puncture needle, taking care not to introduce air; the mixture is now permitted to flow gently into the subdural space. The use of a gauge is not essential, the only requisite being that the quantity removed equal the quantity introduced. If the patient complains of discomfort, the further withdrawal of fluid had best be stopped, and the mixture introduced before the 30 c.c. has been withdrawn. The patient is then allowed to remain in bed 24 hours; in order to facilitate the mixing of serum and spinal fluid, the foot of the bed is elevated about six inches, while the pillows are removed from under the head. As a rule the after-effects are mild, the patient experiencing perhaps some headache; in many instances pains in the lower extremities are felt, in others there may be a feeling of dizziness and perhaps slight fever.

The autoserosalvarsan intraspinal injection method of Swift-Ellis has been adopted by numerous clinicians in this country and in Europe, most of whom have published favorable reports from its use in syphilis of the nervous system, both interstitial and parenchymatous. The original technique as described by the authors has been followed by most men employing this method. But, like every new method, it is capable of modification. In this instance, slight modifications have been introduced both with reference to the time of blood-withdrawal and as to the dilution with normal salt solution. McCaskey believes that because the salvarsan content is rather low an hour after the withdrawal of blood, *twenty minutes* is quite sufficient time to wait before withdrawing the blood. He thus aims to increase the salvarsan content, having seen no ill effects from shortening the period. Because of its simplicity and efficacy this modification has found many friends, the writer of this article among them.

Another modification of the Swift-Ellis treatment consists in the method of injecting pure serum, undiluted with normal salt solution, but otherwise prepared according to the authors' directions, and in the prescribed quantities. My own practice is to use for the initial intraspinal injection 12 c.c. of undiluted serum prepared according to Swift-Ellis, which dose I increase gradually with each injection,—15, 18, 20, 25, and lastly, 30 c.c. of undiluted serum. I have not seen any ill effects from this mode of intraspinal treatment.

DIRECT INTRASPINAL INJECTIONS.—A complicated technique such as the Swift-Ellis method demands is sure to bring forth numerous suggestions at simplification. All attempts were directed towards the introduction of salvarsan and neosalvarsan into the subarachnoid space directly without being under the necessity of first giving an intravenous injection. Wechseltmann was the first to inject a small amount of salvarsan intra-

spinally. He was followed by Marinesco, Ravaut, Schubert, Gennerich, and Wile. Not until Wile had published a concise description of Ravaut's method of direct intraspinal medication had this method been tried to any extent. But no sooner had it become popular, when we began to hear all kinds of unfavorable reports, partly due to defective technique, but mostly to inherent faults of the method itself. Against it must be mentioned the production of paralysis of the legs, bladder and rectal sphincter, as well as decubitus and death. Attracted by the simplicity of this procedure I have given this so-called short cut to success an adequate trial in my hospital work, but like Corbus, Gordon, Sachs, Strauss and Kaliski, I have had unpleasant experiences. Not that I could not record an occasional brilliant result in an almost hopeless case, but the failures were too many and too apparently the result of the treatment. For the present at least, the verdict is against direct intraspinal injections of salvarsan and neosalvarsan. Most of us have already returned to the more complicated—but far safer—autoserosalvarsan therapy of Swift-Ellis.

Ogilvie's Method.—One of the important contributions to intraspinal therapy is that furnished by Dr. Ogilvie, who devised a method of adding small amounts of salvarsan to human serum, prepared according to Swift-Ellis without a previous intravenous injection of salvarsan. The method aims to inject intraspinally a known dose of salvarsan instead of being content with the uncertain quantity of the same remedy contained in a Swift-Ellis injection. While the reports from this treatment are rather encouraging, nevertheless the author sounds a note of warning not to exceed the dose of 1 milligram, owing to the occurrence of temporary bladder disturbances from the larger doses. Fordyce goes even one step further, and thinks the dose of one-half milligram should not be exceeded, as unpleasant sequelae have followed the first-mentioned dose. Swift, in commenting on this method of Ogilvie, admits its greater spirocheticidal effects as compared with his own method, but contends that a certain as yet unexplained principle derived from the patient's blood and probably the result of the action of salvarsan on the blood constituents is lacking in the Ogilvie method, but present in his own procedure of injecting salvarsan into the patient's blood before utilizing the serum.

Byrnes' Method.—This form of intraspinal therapy is similar to the preceding and differs from it only in the fact that to blood-serum, prepared as for Swift-Ellis without the previous intravenous salvarsan injection,—there is added a small dose of mercury bichlorid instead of salvarsan. Dr. Byrnes is under the impression that the beneficial results from the Swift-Ellis treatments are not derived from the infinitesimally small amount of salvarsan contained in the 30 c.c. of diluted serum, but rather from the bichlorid of mercury still circulating in the blood and thus transferred directly into the subarachnoid space. He correctly reminds the reader that salvarsan therapy is nearly always combined with energetic

mercury medication and he therefore proposes the direct introduction of mercury into the subarachnoid spinal space in doses of from one-fiftieth to one-twenty-fifth of a grain (1.3-2.6 milligram). Having tried this method quite extensively in my hospital practice, I am convinced of its efficacy in improving laboratory and clinical findings, but would discourage its further use because of the violent reactions it produces.

INTRACRANIAL INJECTIONS.—By this is meant the introduction into the cranial cavity of spirocheticidal substances either by subdural injection or by placing the remedy into the ventricles. For this purpose the sera prepared according to Swift-Ellis and Ogilvie, as well as Byrnes' bichlorid solution, have been utilized with varying success. One of the greatest enthusiasts for this mode of administering antisypilitic treatment is Henry A. Cotton, of Trenton, who has utilized both the intradural and the intraventricular routes in treating general paresis. In his cases no untoward effects resulted from this procedure. It has been claimed by the advocates of this treatment, especially Drew M. Wardner, who described the intracranial injection of salvarsanized serum in the *American Journal of Insanity* of April, 1916, that the ordinary administration of either mercury or salvarsan, intravenously and intraspinally, does not reach the ventricular system and that therefore the most logical treatment of spirochetal involvement of the brain must be directed to the brain itself. While there may be truth in this statement, there is no great advantage in a method of treatment which has already cost lives and which still presents great technical difficulties. Most of the cases treated thus far have been paretics in a more or less hopeless condition, and for the present the method should be limited to this class of patients.

Iodid Administration.—Not long ago neurologists everywhere attributed great curative powers to the iodids. Especially when treating a case of serious brain syphilis it was the custom to crowd the iodids, even up to one thousand grains daily. Now that we have a gauge in estimating the spirochetal qualities of any drug by means of the several biologic reactions, it has been ascertained that for most forms of nervous syphilis the iodids can be dispensed with. Collins, Weisenburg, and Cotton, for instance, have come out against the use of the iodids altogether, and others are indifferent towards employing them. There are those who, like Jelliffe and myself, having had undoubted proof of the efficacy of iodid medication in the past, are loath to discard its use entirely. While we admit their low spirocheticidal power in attacking the interstitial variety of nervous syphilis, we must concede to the iodids the useful quality of absorption of inflammatory products, the result of microbic activity. It is still necessary to give fair-sized doses of iodids in all forms of vascular syphilis of the nervous system, in which group they have certainly celebrated great triumphs. In my opinion, the dose should not exceed one dram three times daily (4 gm.), largely diluted in water or milk, and

taken after meals. Of course, the iodids constitute a necessary part of the so-called "mixed" treatment, but it is well to bear in mind that the very large doses are not more efficacious than the smaller doses and are more apt to upset the patient's gastric functions. In connection with other treatment I am still in the habit of giving 30-grain doses (2 gm.) of sodium iodid three times daily.

Plan of Treatment.—Almost every clinician has his own favorite method and plan of treatment. All seem to agree that it is essential before beginning any treatment, and even during its continuance, to have the blood and spinal fluid examined for Wassermann, Nonne, and increased cell count. There is no more reliable guide in gauging the progress of treatment and learning something about the extinction of the syphilitic processes than the taking of an occasional inventory of the biologic reactions.

With reference to the use of salvarsan or neosalvarsan, opinions are still divided. When the new preparation was first introduced almost everybody neglected the old salvarsan, for the ease with which neosalvarsan can be injected had much to commend its use. After a short time, however, it was ascertained that salvarsan is much more spirocheticidal than neosalvarsan and that it took many more injections of neosalvarsan than of salvarsan to clear up certain of the early lesions of syphilis. Then came a reaction in favor of the older preparation. Just at this moment public opinion again favors neosalvarsan. Except for the dosage, there is no essential difference between the two forms of salvarsan.

The question of the proper degree of dilution of salvarsan and as to whether concentrated solutions are preferable to the large infusions can and should be decided by each clinician. Personally I have come to regard the dilutions in 200 to 300 c.c. of normal saline solution or distilled water as superfluous and in some instances productive of unpleasant reactions. I prefer in most cases to use very concentrated solutions, which have never given me occasion for regret.

How often shall an intravenous injection be given? In this respect there are also differences of opinion. Most physicians now advocate the "intensive" treatment, that is, the frequent repetition of injections at least in the beginning, widening the intervals later.

Can we rely on salvarsan or neosalvarsan alone, or shall we employ the combined treatment with mercury, or is the mercury to follow or precede the salvarsan? This can now be answered by the statement that salvarsan and mercury given in combination constitute the most effective treatment to begin with. After a series of salvarsan injections the mercury treatment is continued for an indefinite period with the usual intervals of freedom from all medication.

When shall the intraspinal injection of salvarsanized serum be administered in the treatment of nervous syphilis? In the strictly cerebral interstitial lesions it is not at all necessary to resort to the Swift-Ellis treat-

ment. However, in cerebrospinal lues of the chronic variety and especially in tabes the most effective assistance can be obtained from this method of treatment, provided the mercury is also given. Theoretically and practically this method should be the one of choice in the treatment of general paresis. After a perusal of the excellent series of papers by Henry A. Cotton, which were concluded in the January, 1916, issue of the *American Journal of Insanity*, one should feel stimulated to try out both the intraspinal and intracranial injection of salvarsanized serum in cases of general paresis. In his last paper, entitled "The Treatment of Paresis and Tabes Dorsalis by Salvarsanized Serum," Cotton reaches the following conclusions, worthy of citation:

(1) In the use of salvarsanized serum we have an agent which does cause definite arrest in paresis, which arrest includes improvement in the clinical symptoms, physical signs, and a corresponding change in the biological reactions from positive to negative.

(2) To be effective the case must be treated in the early stages, as advanced stages show no favorable reaction to the treatment.

(3) The length of time is not always an indication of the severity of the symptoms, but the majority of cases cannot be helped after two or three years have elapsed.

(4) The treatment must be persistent and uninterrupted, grading the amount of dose and frequency of treatment to the condition of the patient.

(5) Taboparesis should be cautiously treated, usually with small doses, and not oftener than every three weeks.

(6) The remissions caused by treatment cannot be compared to spontaneous remissions, as in the former the percentage is 35.5 and in the latter 4.

(7) The change in the cell count, globulin content, blood and spinal fluid Wassermann reactions are the direct result of treatment, and not to be compared with the variation found in untreated cases of paresis.

(8) The efficacy of treatment depends not on the type of method used, but on the stage of the disease.

(9) Hence the necessity for early diagnosis in paresis, and prompt treatment.

Very encouraging also are the reports of Peter Bassoe, yet to be published, who in verbal communication informed me that after repeated injections by the Swift-Ellis method he has succeeded in returning to useful occupations pronounced cases of general paresis.

R. Dexter and C. L. Cummer report similar results.

It will be inferred from the preceding statements that salvarsan and neosalvarsan have proved our most efficient, and rapidly acting, agents in the fight against brain syphilis, but we must not forget that mercury in its various modes of administration has remained our faithful ally.

Neither must we forget in our enthusiasm to render the Wassermann negative, that we are treating the patient, not the condition of his serum. The patient himself is not at all interested in the laboratory tests,—as Craig and Collins so well put it,—his is the search for physical and mental cure. It will be necessary, therefore, not only to administer directly antisyphilitic remedies, but to employ all the adjuvant measures with which we have so long been acquainted.

[While the newer methods of intraspinal therapy for syphilis of the nervous system have a scientific and anatomic basis and have yielded results apparently more favorable than those obtained by older methods, it seems advisable still to maintain a conservative attitude in promising cure or limitation of the advance of symptoms in any case. Years must elapse before a final opinion can be given. In paresis in which remissions of considerable length may occur in untreated cases, many instances have been noted in which apparently so much longer periods of improvement have been noted following the treatment, as to encourage the hope of permanent cure, but further observation has showed that the course of the disease has been delayed but not completely checked.—EDITORS.]

489. Lines 3-18 *read*:

Etiology.—The **real** cause of general paresis is syphilis, either congenital or acquired. With tabes the disease **was formerly** classed as a **postsyphilitic** disorder, for there is an appreciable interval of time between infection and the development of symptoms—ten or more years. On account of the **supposed** absence of existing specific lesions in brain and spinal cord, and because of the inefficacy of antispecific medication, it **was** thought that the syphilis itself had disappeared, but had left behind toxins. **This view had to be abandoned since Noguchi and Moore discovered the spirocheta pallida in the brains of paretics. W. W. Graves succeeded in reproducing the lesions of syphilis in the rabbit's testicle after inoculation with the blood from paretics. If anything more were needed to definitely establish the true etiology of general paresis, one may cite the almost invariable presence of a positive Wassermann reaction in the blood and spinal fluid of paretics,—a biologic reaction characteristic for syphilis. There may be contributing factors, such as chronic alcoholism, mental strain, or trauma to the head, but the essential cause is syphilis of the brain.**

492. Line 37 *read*:

cure some cases at least. (*See Treatment under Syphilitic Diseases of the Brain.*)

Lines 40-42 *read*:

while others, no less competent, **have seen no real improvement.** Personally, I have **no** hesitancy in recommending this remedy in general paresis **both intravenously and intraspinally administered,** for there is nothing to

493. Line 7 *add* after "salvarsan.":

The so-called Swift-Ellis treatment finds here a field for experimental activity. Likewise direct intracranial injections of salvarsan and neosalvarsan have been practiced mostly with results that warrant further trials.

Lines 18-19 *read*:

Whatever treatment may have been selected—mercury, salvarsan, or **salvarsanized serum injections, intraspinally**,—it is

494. *Substitute* for "References.":

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CHAPTER XVI

DISEASES OF THE PONS AND MEDULLA

JULIUS GRINKER

511. *Add* under "References.":

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CHAPTER XVIII

NEUROSES

NEURASTHENIC AND PSYCHASTHENIC STATES, INCLUDING THE PHOBIAS

LEWELLYS F. BARKER AND CHARLES M. BYRNES

517. Line 44 *add* after "apparatus." :

They make up the large contingent known as false gastropaths, false enteropaths, false cardiopaths, etc.

519. Line 30 *add* after "*(Verdrängung)*." :

A strong reaction against the Freudian teachings has set in, and though all admit the great importance of sexual instinct in connection with many of the psychoneuroses, the majority of neurologists incline to the view that Freud and his stricter adherents have given overemphasis to sex, to the neglect of other fundamental instincts.

Line 42 *add* after "abnormality." :

Long converted to the doctrines of physical hygiene, medical men have been slow to awaken to the importance of mental hygiene, perhaps because this was formerly thought to belong in the domain of the clergyman and of the schoolmaster rather than in that of the physician.

The more we study the psychoneuroses, the more we become convinced of the importance of the affective life—the life of the emotions and sentiments—for their pathogenesis. Emotions are an essential part of life; they cannot be avoided; indeed human life without them would be undesirable, even if it were possible. The mischief lies most often in a lack of harmony and of unity in the personality as a whole, made up as it is of cognitive, affective, and conative elements. Anything that we can do (1) through *heredity* to develop human nervous systems capable of a full and harmonious development of the intellect, the emotions and the will, and (2) through *environment* to bring to bear upon the nervous systems the influences that will be helpful, preventing, as far as possible, the action of influences that we know can be harmful, will be a contribution toward the prophylaxis of the psychoneuroses.

Experience teaches that those persons that become absorbed in the attempt to work toward the realization of an ideal—practical, religious or philosophic—are far less prone to nervous breakdown than those that have no definite aim in life, no unitary direction to their thoughts, feelings and activities; nothing, in other words, sufficiently adequate to integrate the divers constituents of a personality.

522. Line 1 *add* after “principles.”:

Children that manifest a preternatural emotivity should always cause concern to the observant family physician. A child that has too lively vasomotors, reddening or turning pale on slight provocation, or one that goes too easily from exuberance to sadness, will attract his attention and lead him to give special directions to the parents regarding supervision, physical, mental, and moral.

Line 25 *add* after “children.”:

In connection with functional nervous disorders in childhood, the physician may consult L. G. Guthrie’s “Functional Nervous Disorders in Childhood,” V. M. Hillyer’s “Child Training,” L. F. Barker’s “Principles of Mental Hygiene Applied to the Management of Nervous Children,” H. Oppenheim’s “Nervenleiden und Erziehung,” and G. W. Jacoby’s “Child Training as an Exact Science.”

523. Line 29 *add* after “disorders.”:

In the education of youth, care should be taken to combat sentimentality, timidity, hypersensitiveness and indecision. In the choice of a career, the natural powers of the person as well as his environmental opportunities should receive due consideration. Self-confidence should be developed and maintained by suitable adjustment of activities within limits set by heredity and surroundings. Stewart Paton’s suggestion that college students have free access to an adviser endowed with common sense and trained in psychiatry is worthy of serious consideration by educational authorities.

524. Line 33 *add* after “stage.”:

Emotion as a cause of neurasthenia may have either an external or an internal origin. Thus, among the *external* cases, railway or motor accidents, the sudden death of one near and dear to the person, a great financial loss, a dishonorable act by some near relative are common examples. Sometimes, an unexpected joy will be operative—a proffer of marriage, a great bequest, a lucky turn in the stock-market—especially if it comes to a mental make-up that cannot quickly and adequately adapt itself to the new situation. Among the *internal* may be mentioned the memory of an earlier shock, and the harboring of ideas accompanied by strong emotional tone (e.g., the idea of death, or invalidism, of ruin, of dishonor); especially, when the mind does not adapt itself to the idea, but revolts against it and continually preoccupies itself with it, is the

emotional result harmful. Such emotion is oftentimes followed by symptoms that the patient attributes to a local physical origin (e.g., pseudo-angina, feelings of suffocation, epigastralgia, feelings of general anxiety, dyspnea, diarrhea, or pollakiuria); the physician without psychiatric training may, in such cases, easily overlook the psychic trouble antecedent to the physical complaint. It is very helpful to a practicing physician to know as a result of long acquaintance with a person what the ordinary degree of emotivity for that person is. The family physician has exceptional opportunity for learning the degree of intellectual control possessed by his patient; he, too, should be best able to make an objective report on the general character of a patient, for if he be alert to these things he will have recognized any lack of self-confidence, any hypochondriacal tendency, or any moral uncertainty, overconscientiousness, or excessive scrupulosity that may have existed.

The exciting emotional cause of a neurasthenic state should be diligently sought and its full avowal encouraged. Physical causes predisposing to pathological emotivity should also be sufficiently valued; it seems probable that influences like overwork, fatigue, and undernourishment help to create a favorable soil in which pathological emotivity grows. But to attribute the origin of a psychoneurosis to them alone without consideration of the psychic factors, would be like trying to account for the origin of tuberculosis without considering the necessary presence of the tubercle bacillus. As Déjerine and Gauckler put it: "*Sans émotion il n'y a pas de psychoneuroses. Sans la genèse des états nevropathiques, il existe toujours une cause émotive.*" Indeed, they define neurasthenia as a state constituted by "the totality of phenomena that result from the nonadaptation of the being to a continued emotional cause and from the struggle of the being for that adaptation."

525. Line 2 *read*:

similar external conditions? **In what degree is each of the several fundamental instincts represented in the patient before us?** The exact physical answer to these questions

Line 32 *read*:

of **any** abnormal physical condition **that may be a contributory factor.** If detected, ra-

526. Line 3 *add* after "relationships.":

In practically every case, a careful research will reveal the existence of some emotional experience to which the personality has been unable to adapt itself.

Line 6 *read*:

and may entail much work, including **several conversations** and the making of **many physical and** laboratory

Line 20 *read*:

almost wholly to general upbuilding treatment **and to psychotherapy**.
We feel that, in this con-

Line 41 *read*:

men—internists, surgeons, **orthopedists**, rhinologists, gynecologists, neurologists, etc.—

5.8. Line 14 *add* after “apprehension.”:

If the patient can be led to make a frank and full avowal of the emotional experience that has been, perhaps unconsciously, the main cause of his nervous state, the best possible start will have been made.

Line 17 *read*:

structions faithfully. In some instances **in addition to the psychotherapy that must always be our main effort**, a short vacation may suffice, or

Line 44 *add* after “instructor.”:

Medical students should have larger opportunities than have hitherto been available for the study of the psychoneuroses and for gaining experience in the practice of scientific psychotherapy.

530. Line 11 *add* after “avoided.”:

(4) In all the *severer forms of psychoneurosis*, the patient should be removed entirely from his ordinary occupations and his usual surroundings. He should be placed in a hospital, sanitarium, or nursing home, where he may have the best form of *psychotherapy*, together with its necessary adjuvants, namely, *isolation, rest, and abundant food*.

531. Line 10 *add* after “real.”:

It is usually easy, even for a young physician if he has learned how to do it, to gain the confidence of a neuropathic patient at the first interview, for the neuropath readily gives his confidence to a physician that shows an interest in him, that will listen patiently to his complaints, and that will show by his questions and his statements that he has a real understanding of, and sympathy with, the sufferings of the psychoneurotic. Great care should be taken not to commit one's self to a diagnosis, to a prognosis, or to a form of therapy, before the patient has been thoroughly studied from all sides—physical and psychical. Not only should the patient be encouraged in the beginning to mention all his complaints, to relate all his experiences with former treatments, and to give expression to his own theories of his condition and its causes, but the physician should go farther and inquire specifically about all the bodily and mental functions, including especially those to which the patient himself has made no reference as well as to those he has specifically emphasized. Only in this way will the patient be convinced that the physician's examination has been thorough and complete. Moreover, full notes should be recorded of the patient's statements and of his answers to questions, for these notes

may prove to be of the greatest value to the physician later on in his therapeutic management of the case. The physician should never stop short of the most important part of the questionnaire, namely, that bearing upon the emotions, or worries, that have been the exciting cause of the neurosis.

He must not hesitate to inquire into the most intimate facts of the patient's life, including his love, his religion, and his philosophy. He will of course vary his interrogatories with the character, the mental make-up, and the education of his patient, though he will not forget that the fundamental instincts are common to all human beings and that the thoughts, emotions and acts that pertain to each instinct are similar in all:—"The captain's lady and Julia O'Grady are sisters under their skins!"

Line 35 *add* after "inspired.":

After some experience, the physician learns how to use the different forms of psychotherapy and when to apply each form. He must know how and when to command, how to lead a patient to forget, how to change the course of ideas by suitable distraction, above all how systematically to re-educate the patient so that he may lead as nearly as possible a normal life. Each patient's personality must be studied thoroughly and the treatment varied accordingly. Age, sex, character, education, social opportunities, religion—all should be considered when deciding upon the general course to be followed and the detail of management in a given case.

532. Line 22 *add* after "it.":

If the patient has been cared for by a nurse when she applies to the physician for treatment the question of retaining that nurse or of starting afresh with a new one should be considered. Each instance will require its own decision, though as a rule it is better to begin with a new nurse.

Line 39 *add* after "discussed.":

We must emphasize the fact, however, that he who relies mainly on physical methods of treatment of the psychoneuroses will fail very often. The physical methods of treatment are very valuable as adjuvants, but the main effort in treating neurasthenia and psychasthenia should be directed towards influencing the minds of the patients, that is toward psychotherapy. This psychotherapy should rarely be one of argumentation; it should rather be one of creation of confidence in a physician, who will then lead the patient to have confidence again in himself. To succeed, a physician must be able to make his patient "like him"; sentiment is an important factor in the establishment of an atmosphere of confidence, for as Déjerine has well said: "*Ancune idée n'est admise à froid.*"

533. Line 16 *add* after "stimulation.":

Weir Mitchell also recognized the importance of psychotherapy in the treatment and was a master in the art of practicing it.

535. Line 2 *add* after "necessary.":

It should be remembered that in nearly every case it is mental rest that the patients need even more than physical rest. The problem of how to secure this mental rest is the one that throws the heaviest tax on the physician. In severe cases it can scarcely be secured without isolating the patient.

536. Line 12 *add* after "experiences.":

Isolation should be looked upon, not as an end in itself, but as Déjerine and Gauckler emphasize, only as a means to an end, a means absolutely necessary in many instances for the continuous and successful application of psychotherapy.

537. Line 36 *add* after "it.":

By far the majority of patients can and will take milk, even in large amounts, if the physician requests it, gives his assurance that it may be taken without harm, and urges the patient to continue its use despite any symptoms that may follow its ingestion and that he may be inclined to attribute to it.

538. Line 33 *read*:

crackers, or milk. **In most undernourished patients, three large meals should be taken, and in addition four to six glasses of milk and three to six raw eggs per day; the latter are best taken immediately after the three main meals, not between them.** Forced feeding is often used for too long a period,

540. Line 43 *add* after "Treatment.":

DÉJERINE AND GAUCKLER DIET FOR PSYCHONEUROTIC PATIENTS

These authors prefer a milk régime, either partial or absolute, for the majority of their patients undergoing psychotherapy. Déjerine asserts that true intolerance for milk does not exist in more than one patient out of two or three hundred. Admitting that bloating, bad taste in the mouth, diarrhea or constipation may at first be complained of, it is found that these symptoms last only a few days and may therefore be ignored.

Déjerine and Gauckler give hourly doses, for twelve hours each day. They give 250 c.c. per hour for the first day, that is 3 liters, and soon increase the amount to 3½, 4 or 5 liters per day, this maximal amount being reached by the eighth or tenth day of treatment. The patients gain rapidly in weight—one and a half to four or five kilograms per week.

This milk diet is continued until the patient's normal weight is attained, after which an ordinary wholesome mixed diet is given.

543. Line 32 *add* after "papers.":

After breakfast, swallow one or two raw eggs.

Line 38 *add* after “-ness.”:

After luncheon, swallow one or two raw eggs.

Line 42 *add* after “coffee.”:

After supper, swallow one or two raw eggs.

544. Line 30 *read*:

Dubois and **Déjerine** are among those that have tried to establish its use on a solid basis.

Line 32 *read*:

period of twenty years, **they** gradually came to attach less importance to

Line 35 *read*:

attitude in the patient. **Dubois** modified gradually the degree of isolation

546. Line 33 *add* after “massage.”:

The attentions of a good hair-dresser are often helpful. Sometimes the application of a vibrator to the scalp, face, and neck will be found to be a useful adjuvant in treatment.

549. Line 7 *add* after “consulted.”:

We would especially warn against being “overbusy” in hydrotherapeutic applications. We have known patients to be seriously fatigued by the overzeal of ardent hydrotheraputists.

550. Line 3 *add* after “surprising.”:

The psychotherapy for these patients should be divided into two parts: (1) that directed toward the underlying mental state of the patients, and (2) that directed toward the functional manifestations of which the patients complain. In treating the underlying mental state, the physician will endeavor to restore the integrity of the personality chiefly by encouraging *avowal* and in developing the *conviction* that cure is possible and will do all he can to *free the patient* from the emotional preoccupations that have been responsible for his state. In treating the functional manifestations, the psychotherapist will *examine, interpret, reassure, teach to ignore, teach to forget*, and in general, *reëducate* to normal life.

Line 20 *add* after “instructor.”:

The exercises described in R. F. McKenzie’s “Exercise in Education and Medicine,” in J. F. Muller’s “My System” and in Sanford Bennett’s “Old Age; Its Cure and Prevention” may be found useful in planning a régime.

552. Line 12 *add* after “list.”:

The young physician desirous of training himself in psychotherapy will find much that is valuable in Weir Mitchell’s writings, in Camus and Pagniez’s “Isolement et Psychotherapie,” in P. Dubois’s “Psychic Treatment of Nervous Disorders,” in Déjerine and Gauckler’s “Psychoneuroses and Their Treatment by Psychotherapy,” in W. R. Duntton’s “Occupation

Therapy," in R. C. Cabot's "What Men Live By," in P. Janet's "Les Obsessions et la Psychasthénie," in H. Oppenheim's "Letters on Psychotherapeutics," in A. Gross's "Allgemeine Therapie der Psychosen," in E. H. Itschmann's "Freud's Theories of the Neuroses," in June's "Psychology of the Unconscious," and in McDougall's "Social Psychology,"

555. Line 16 *add* after "astronomy.":

Nurses in charge of nervous patients would do well to familiarize themselves with the contents of W. R. Duntton's excellent manual entitled "Occupation Therapy," and of Hall and Buck's volume "The Work of Our Hands."

557. Line 44 *read*:

of drug treatment may sometimes, **though rarely, in our opinion,** be valuable for its psychic effect. But

559. Line 4 *read*:

gain in body weight, **since arsenic, like quinin, retards metabolism.**

560. Line 3 *add* after "faradism.":

AVOIDANCE OF DRUGS.—On the whole, we urge that drugs should be avoided in the treatment of psychoneuroses, even as palliative measures. As a rule the use of drugs in these maladies is an abuse of the credulity of the patients. Moreover, drug treatment is here rarely efficacious, aside from the accompanying danger of aggravating the psychoneurosis. The physician who begins to treat the headache of the psychoneurotic with acetanilid, his insomnia with veronal, his indigestion with pepsin, his fleeting pains with aspirin, his asthenia with strychnin, or his constipation with cascara, reveals either his forgetfulness or his lack of knowledge of the nature of the disorder and its proper therapy. Many neurasthenic patients carry a small drug store about with them, and one of the first duties of the physician that understands the psychotherapy of neurasthenia consists in weaning these patients from their drug habits. Let him who is in doubt in this matter read the very amusing description by Brian Borum Dunne, entitled "Cured! The Seventy Adventures of a Dyspeptic," and one may even doubt this highly credulous author's interpretation of his final "Cure!"

561. Line 2 *add* after "(Kolonie Friedau).":

Déjerine's work at the Salpêtrière in Paris has attained to well-merited fame, as has also the work of Dubois at Berne.

562. Line 40 *read*:

yield to the protective measures previously outlined, **and to a carefully planned and executed psychotherapy,** and we feel that in

563. Line 7 *add* after "cases.":

We must treat the patient as a whole, but the mistake most often made is

to neglect general psychotherapy and to overemphasize local and special therapeutic measures.

Line 12 *add* after "states.":

Unfortunately, we are as yet ill-informed regarding the physiology of sleep. Certain facts seem established, namely, the relations of sleep to (1) the needs of the vegetative life of the inner organs, (2) peripheral excitation of the organs of sense, and (3) the excitations of the mental life. Habit certainly has a great deal to do with (1) the feeling of the need of sleep and the origin of the idea that we should go to sleep at a given time, and (2) the duration of sleep and the reawakening at a given hour. People vary in their methods of going to sleep and in their methods of awaking. Some go to sleep at once, the moment their heads rest on the pillow; others read themselves to sleep, or go gradually to sleep after counting sheep going over a stile. Some at the moment of awaking are wide-awake; others awake gradually, not becoming wide-awake for some little time (minutes or hours), or until after a cold shower and a rub.

Line 44 *add* after "hypertension.":

Some neurasthenics pass through periods when they actually do not sleep at all—the insomnia is absolute. This is, however, rare. Many patients, though they sleep from six to eight hours, assert that their sleep does not rest them, that they feel more tired in the morning than they did on retiring.

In persistent insomnia, a careful study of the psychological automatism of the patient should be made, for here will be found the thoughts, the emotions, and the preoccupations that either prevent the patient from going to sleep, or account for his untimely reawakening or for the dreams that disturb his sleep. It is here that a full avowal on the part of the patient to his physician may bring the needed liberation. Sometimes an elaborate psycho-analysis may be necessary in order to bring the full avowal. As a help in such psycho-analysis, the physician may study Freud's "Interpretation of Dreams" and Jung's "Psychology of the Unconscious."

564. Line 6 *add* after "insomnia.":

This consists chiefly in the judicious use of psychotherapy and its adjuncts (isolation, rest, diet). Certain physical details should not be neglected.

Line 15 *add* after "harm.":

We consider it very important to reorganize the life of the patient so as to reëducate him to normal sleep. Thus certain hours of the twenty-four are to be set apart for sleep and to be used for no other purpose. We teach the patient (1) to go to sleep at a certain time, (2) to expect sleep then, (3) to try to banish thought during sleeping hours, (4) to decide to lie quietly (though *not* rigidly immobile!) and rest even though he

does not sleep, (5) to try not to care whether he sleeps or not, and (6) to avoid getting up and walking about, or reading, in case sleep does not come. Usually with mild hydrotherapy, rest, and, in severe cases, isolation, the insomnia gradually yields.

565. Line 1 *read*:

The drug treatment of insomnia should be a last resort, **and even then should be used only as a temporary measure**; one should keep

Line 42 *read*:

neurasthenic complaints. **But, in our opinion, it is upon general measures, and especially upon psychotherapy, that we should mainly depend.**

The general tendency of physicians is to try local physical treatment for these functional manifestations. Thus in the various treatises we are told that massage, either general or local, manual or

566. Line 16 *add* after "harmful.":

In our experience it has been found much more satisfactory to avoid local and drug therapy for headache and psychalgias. We first make sure of his personal hygiene; then we reassure the patient, by telling him that there is no danger from the symptoms, that when he is better the symptoms will disappear, or at any rate be less troublesome, and teach him to bear stoically what he has to bear in the meantime. It is surprising and most gratifying to see how quickly and permanently the symptoms disappear under this form of therapy in the majority of cases.

Line 26 *read*:

to defecation at a definite hour each morning, **preferably immediately after breakfast**, should be established. A

Line 39 *add* after "Constipation.)":

Constipation nearly always disappears under an abundant diet and general psychotherapy, especially if local treatments and purgatives of all sorts are *taboo*.

Most people who complain of constipation think far too much about the functions of their intestines. Once one has ruled out an organic cause, it is best to give an abundant diet, insist on a regular time to go to stool each day, improve the general mental emotional state of the patient, and teach him to forget his intestines.

Lines 43-44 *substitute*:

to eat even in the absence of appetite. In outspoken anorexia, and especially in severe cases of mental anorexia (anorexia nervosa), rigid isolation is essential. It is rarely, though it may be occasionally, necessary to feed the patient by stomach tube.

567. Lines 1-11 *read*:

The patient simply must be fed, whether he has appetite or not. Many failures occur because the physician does not isolate the patient, because

he has not the right kind of nurse to aid him, or because he has not learned to persuade the patient or to use his authority. The vomiting of psychoneurotics may be controlled by psychic treatment (**isolation**, reassurance, and encouragement in the effort to retain small amounts of nourishment given at frequent intervals).

Line 11 *add* after "established." :

One of the commonest symptoms met with in the treatment of functional nervous states is the fear of the patients that certain foods which everybody eats cannot be tolerated or digested. The patients often cut off one food after another until they are literally starving themselves in the hope of curing their "indigestion." Such gastrophobic patients may be very easy, or they may be difficult to manage. If the fear is not too firmly established, a full mixed diet, regardless of choice, may be given at the end of a week of milk diet, and with success. In severe forms, a slower method has to be employed, the patient being gradually reëducated to eat all foods despite their fears. In the worst cases in which there is marked emaciation it is often wise to give a milk diet alone until the normal weight has been reëstablished. Beginning with small quantities of milk every one or two hours for twelve hours each day, the amounts are increased until the patient takes four or five liters of milk every day. In a few weeks the patient's weight may be normal and the physician may then start in to train the patient to eat all kinds of food. Throughout the whole period, the psychotherapy of the general state of the patient should be given careful attention.

Line 14 *read* :

In either case rest is essential. Loss of sleep is a common cause of fatigue, **so also is the worry and the preoccupation of these patients.**

Line 16 *add* after "contraindicated." :

On beginning the return to activity with these patients care must be taken to reëducate them to exertion without their realizing it. We keep the attention of the patient fixed upon the amount of rest he is to take each day, rather than upon the amount of the exertion. As regards the latter, we tell the patient not that he must walk so much each day, but that he is not to walk longer than a certain time; in other words, we limit the exertion to a maximum and do not fix a minimum.

Line 21 *add* after "weak." :

In our experience, however, it is better to overcome the symptoms without the use of drugs. In the long run, success will be far greater.

568. Line 5 *read* :

used to advantage. Psychotherapy is **the most important factor in the management of these cases.** We explain to the patient the nature of his trouble, assure him that he may safely ignore the symptoms, forbid him

to count his pulse himself and do all we can to distract his attention and to allay his apprehension; drug treatment

Line 16 *read*:

upon either side. **The symptom is sometimes a sign of slight hyperthyroidism.** The condition is aggravated by the reclining posture

Line 39 *add* after "people!":

Anomalies of Micturition.—Frequent micturition (pottiakiuria) is often complained of. Others assert that urination is painful or accompanied by a "queer sensation." In such cases, the urine should be carefully studied and a thorough local examination of the urethra and bladder made to rule out a urethritis, a cystitis, a prostatitis, or a nephropathy. If a genito-urinary specialist is called in consultation in a psychoneurotic case, he should be told in advance of the abnormal mental state of the patient and asked to report not to the patient but to the physician. Undoubtedly there are cases that require local treatment and this should then be instituted. But far more often no local treatment whatever is required and, instead, is distinctly contraindicated. Every neurologist is familiar with the prostatophobe who has suffered weeks or months of prostatic massage without benefit when his trouble was not in his prostate but in his "head." Such patients need reassurance and a total cessation of local therapy.

Genital Disturbances.—Among male psychoneurotics, disturbances of libido erection, ejaculation, and orgasm are very common. The physicians at Niagara Falls, at Atlantic City and other resorts of honeymooners are very familiar with such phenomena in the newly-wed. But also before and even long after marriage, functional disturbances of the genitals are common, and are often very troublesome in management.

In women, too, functional genital maladies are very common, and the physician that treats psychoneurotic cases dare not be blind to them. One of the main causes is the ignorance regarding sex-matters with which girls are allowed to grow up and with which young women often enter the married state. One is frequently astounded at the false ideas that prevail. Fear of the physical side of sex and disgust with matters sexual are often systematically cultivated, to the great harm of these persons. Vaginismus, frigidity, or coitus interruptus may be important factors in the exacerbation of nervous states. The physician will get much help from the study of Havelock Ellis's "Psychology of Sex" (in six volumes) and of Déjerine and Gauckler's "Psychoneuroses."

570. Line 35 *read*:

Freud, of Vienna, and (5) that of Déjerine of Paris, are among the better known.

572. Line 2 *add* after "based.":

Déjerine and Gauckler emphasize the importance of not expecting

more from psychotherapy by persuasion than the method is capable of yielding. They point out that the mental mechanism must be fairly healthy for persuasion to be applicable, for attempted in imbecility or in organic disease but little can be expected from it. They assert, too, that there is not psychotherapy in the sense in which they use the term for the marked obsessions for true melancholia, for circular insanity or for the other insane. When psychotherapy has seemed to be helpful among the actually insane, they ascribe it to its application at a time when a natural or spontaneous remission was occurring.

TREATMENT OF HYSTERIA

SMITH ELY JELLIFFE

582. Lines 16-19 *read*:

No unanimity of opinion has ever been reached, **yet there are numerous evidences to show that some settled basis is being formulated.**

583. Line 13 *add* after "factor.":

Stated all too didactically neurasthenia here means nerve fatigue, due to a definite and ponderable factor. There must be some concrete toxic or infectious or overwork factor, not a hazy surmise but a real thing, a typhoid, influenza, lead, syphilis or similar outside agent. The anxiety neurosis group is made up of patients who are also suffering from definite thwarting of the instinct of reproduction. Crudely stated they are struggling with sexual repressions which are not very unconscious and they are unable to handle them at higher social levels and hence with the concrete mechanical factors noted get sick.

585. Line 25 *add* after "later.":

It is further useful to utilize Jung's concept of extroversion and introversion types in this sizing up of the differences between schizophrenic and hysterical reaction types. The typical schizophrenic is introverted. His working energy (libido) is devoted to self, to internal contemplations, to early auto-erotic and narcissistic satisfactions. The hysterical mechanism is a direct antithesis (ambivalent). Here extroversion of the libido is the mode followed for solving the mental conflict. The hysterical has, therefore, much free floating libido to attach to the external object. Inasmuch as this object is more often the physician than anyone else it is highly important to understand this phase of the hysterical mechanism.

Line 31 *read*:

valid nosological group—any more than "ascites," "headache," or "jaundice."

586. Line 2 *add* after "another." :

A severe hysteria is frequently mistaken for a "melancholia." Only an extremely sympathetic attitude towards mental facts will enable one to get at the real issues.

Lines 3-4 *read*:

Association tests, **frequently** reveal the **faulty** mechanisms. It is impossible in this place to enumerate the

Line 24 *add* after "considered." :

Real feeble-mindedness is here viewed from the aspect of structural defect. There are many pseudofeeble-minded wherein the difficulty is due chiefly to emotional blocking. There is no real anatomical defect, the disturbance is truly functional. These cases are best grouped with the hystericals rather than with the feeble-minded. Many very brilliant minds, struggling in adolescences with large psychical problems, have been diagnosed by stupid pedagogues as feeble-minded. Later they have overcome their difficulties and become large figures in the world of science, politics, etc.

Line 42 *read*:

tion by Freud, nearly all of the studies on hysteria **failed to arrive at a definite dynamic conclusion and hence were on the way rather than arriving.**

587. Line 38 *add* after "relief" :

Thus if the transference is temporarily fixed upon a gynecologist, the symptoms will be gynecological, if a surgeon, surgical, dermatologist, dermatological, etc., etc. The classical hysteria collection of conversion symbols will box the medical compass. This is the explanation of the old and well recognized fact, that hysteria "mimics all diseases." It also explains why all forms of therapy will show successes. But these are purely the result of superficial rapport. They are a symptom but do not modify the capacity for making new ones.

Line 43 *add* after "(also 5)" :

The point to be emphasized then is that the term hysteria is reserved for a special form of conversion mechanism. The libido of the patient in its endeavor to extrovert, to get attached to some external object, that is to establish a transference (rapport), creates, through some somatic channel, an object of interest, i.e., the symptom. This symptom is usually symbolic of the conflict and it is capable of countless modifications, according to the transference needs.

588. Line 10 *read*:

tricacies of the psychoanalytic method. Such **feeble-minded or stupid** persons are most effectively

589. Line 6 *add* after "instrument." :

Without the psychoanalytic viewpoint the dynamic evolution of the situa-

tion cannot really be uncarthed. Anything short of complete (i.e., practical) comprehension of the patient's conflicts and their resolution by analysis leaves the patient in much the same condition as before treatment.

591. Line 19 *read*:

and vomiting isolated paresthesia, attacks of giddiness or vertigo, **transitory palsies, intest-**

592. Line 24 *read*:

Occasionally salicylic **acid** derivatives and other members of the group are

593. Lines 31-33 *read*:

would not be so reprehensible, as in certain very old individuals. **The patient himself should never be intrusted with morphin derivatives.**

594. Lines 16-17 *read*:

"If it be assumed that the hypothesis outlined, i.e., **that the migraines are mostly vasomotor neuroses, is valid**, it is essential to search out

Line 19 *read*:

of the vascular control held by the **vegetative** nervous system. A great

Line 28 *read*:

somatic defects.

596. Line 13 *add* after "few.":

Increasing experience with migraine is tending to show the so-called predisposition to migraine is only one of the many variants of the neurotic constitution. Migraine for these is the somatic scapegoat of the unconscious conflict. Such migraines, therefore, which have defied therapy for years, may be successfully combated by the psychoanalytic mode of approach. The patient thus analyzed, while he may not always rise above his conflict and hence may occasionally need his somatic scapegoat, may get to comprehend wherein he handles his conflicts badly and thus can avoid severe attacks particularly.

Line 31 *read*:

species **of headaches** make a veritable Garden of Allah.

598. Line 4 *read*:

Not infrequently an antecedent influenza, malaria, **typhoid**, or other

Line 7 *read*:

kemia and diabetes are **occasional causative factors.**

599. Line 35 *read*:

may bear in neurotic types some proportional ratio to the intensity of the visceral disturbance. **These pains may be severe.**

Line 44 *read*:

The accompanying figures illustrate the main **localizations.**

605. Line 15 *read*:
certain. **It is highly probable they are vegetative nervous disorders of the nature of tissue edemas.**

Line 31 *read*:
of the malady has been forgotten by most doctors of the scientific era, **the osteopathic ideas of etiology, however, are absurd. The good results come from deep massage of the nodules.**

607. Lines 1-3 *read*:
The blood Wassermann is **usually positive**, the cerebrospinal Wassermann **may be negative**, and Phase I Nonne not yet definitely known; **the cell count is apt to be variable but usually some lymphocytosis is present.**

610. Line 1 *read*:
may be allowed to remain, permitting a few c.c. **of the cerebrospinal fluid to escape every minute**

612. Lines 2-3 *read*:
passage has an obvious effect upon the circulation and the **vegetative circulatory mechanisms of the splanchnic area.**

613. Line 10 *read*:
sistance to more fundamental causes for **somatic headache.**

614. Line 8 *add* after "headache.":
Unsatisfied phantasies often combined with concrete masturbatory activities are very widely found in true neurasthenic and in anxiety neurosis headaches. It must be remembered that genital masturbation is not the only type of self-worship and self-indulgence. Every sensory area is capable of masturbatory activities.

Line 32 *add* after "headaches.":
Psychoanalysis is rarely needed in the pure types.

615. Lines 30-31 *read*:
thenic phases. **Psychoanalysis, most carefully conducted, alone attempts any real "getting at" these patients.**

616. Line 7 *add* after "eration.":
Nominally included here as neurosis, the present discussion deals with all types of vertigoes.

630. Line 8 *add* after "faddists.":
Ocular vertigoes from arteriosclerotic disease in the aged are frequent. Here eye nuclei pathways are involved in thrombotic softenings.

Line 22 *add* after "neurosis.":
This frequently found syndrome is best treated by careful readjustment of the sexual aims of the patient. Sexual is here used in the broadest sense.

634. Line 26 *read*:

of the text-books of Oppenheim, Starr, Lewandowsky, **Jelliffe and White**, and the Osler and

638. Line 27 *add* after "simulation.":

The Dynamics of the Epileptic Attack.—The clinical syndrome of the epileptic attack in its many variations has become clearer and clearer with each generation of observers. It has broadened a great deal since its earliest descriptions by Hippocrates, and furthermore from the anatomical and chemical sides a much deeper study has shown a multiplicity of lesions in the brains of individuals suffering from epileptic attacks. These anatomical and chemical findings, well summarized by Munson in White and Jelliffe's large volumes on the "Modern Treatment of Nervous and Mental Disorders" (1913), most strikingly reveal in how many different and various ways the motor pathways in the brain may be involved. Notwithstanding this richness of clinical delineation, and this array of findings on the anatomical and chemical sides, there still remain to be stated some definite functional fundamentals which will render the attack intelligible. A brief presentation of the dynamics of the discharge is therefore essential.

The human organism, like all other living organisms, has built up a rich system of mechanisms to adjust itself to the problem of living. The human varies solely in his richness of contacts and his wealth of reactions. The entire biological series has its culmination in man. Lower organisms are adjusted to simple physicochemical surroundings through a series of mechanisms which have been termed tropisms. Higher organisms have established interrelations between these tropisms by means of a nervous system which acts through a series of reflexes. Finally all those higher animals have established psychical or mental processes for purposes of socialization. Man, as a social animal par excellence, has built up a rich and varied series of intercommunications and interrelations through his language symbols.

The human nervous system therefore may be viewed as having evolved gradually through a series of ascending phases, which for purposes of description may be limited to three levels: a level of physicochemical adjustments, which is taken care of by the vegetative nervous system (sympathetic in a larger sense), the sensorimotor system (cranial and peripheral nerves), and a psychical or mental system functioning by utilization of symbols.

The function of the body as a whole is to transform energy for its own purposes. This energy is the cosmic energy which is derived from the sun and is known under a variety of forms, such as heat, light, electricity, chemical action, gravity, etc., etc. It must not be imagined that the only energy that the human body can transform is the chemical energy

of food. This is the smallest part of the work done by the human machine, and so far as may now be seen, the food energy is solely utilized in the upkeep of the machine. The energy for instance which was, is, and will be transformed by the Gettysburg speech cannot be computed in terms of Lincoln's breakfast eaten on the day of that memorable occasion.

It is essential to realize in studying the epileptic problem, as well as any other in which motor activity is to be interpreted, that the dynamics of energy transformation is not to be understood solely in terms of the lowest of man's adaptive levels, i.e., the physicochemical or metabolic level. The chief energy transformer at this level is the "hormone"; for the sensorimotor level, the reflex; while for the psychological level, the symbol is the energy transformer.

Now viewing the human animal from the structural viewpoint and reducing the nervous system to its simplest terms, man may be thought of as consisting of a group of receptors, or receiving organs, whereby he comes in contact with, that is, receives energy from the external world, as outside of himself (exteroceptors) and as part of himself (proprioceptors). The combined material falling upon these receptors, must be reacted to in some form and thus there results a series of effectors to carry out the necessary adaptation—control of nature. These effectors are chiefly muscles, striped and unstriped, working consciously or unconsciously, but other effectors are glands, etc. In the highly complicated organisms, with rich compound reflex systems, such as in man, a host of switchboard connections is developed—relators or connectors. These are, as is well known, extremely complicated and make up the chief mass of the spinal cord and brain. The old view that the ganglion cells stored up energy, or were repositories of energy or made energy, must be abandoned. That they have such as an accessory function related to their own maintenance as working structures may be, but they are not to be viewed in the old Leyden-jar analogy sense as independent sources of energy.

Thus the nervous system is to be viewed as a mass of interrelated pathways which through hormone, reflex, and symbolic transformers redistribute and modify the energy received for the purposes of the organism.

A well adjusted nervous mechanism then is one that properly and in an orderly fashion can distribute its energy, but an epileptic organism is one, as already pointed out, that is constantly breaking down in its adjustments and that creates disturbances at the various levels just enumerated. Thus it can be understood that an epileptic attack can more or less limit itself to any one level. It may all be metabolic, or sensorimotor (classical attack), or a purely symbolic attack (psychical equivalent). As a rule, the well developed attack involves all three levels. Thus there are so-called hysterical convulsions which involve only the highest levels. From the viewpoint here adopted these are purely psychogenic. The mental or symbolic energy is converted into physical phenom-

ena—the convulsive seizures. The patient escapes from a painful adjustment of his difficulties (energy distribution) through a flight into a lower level—i.e., from the psychical to the physical. The careful student of hysterical convulsions by studying the effector actions (motions) will be able to determine precisely through what channels the blocking of the energy has taken place and wherein the energy has been discharged in a more diffuse manner.

In the compulsion neurosis, convulsive attacks appear which are of a lower type. They resemble the severe, all-level attacks more closely, but energy discharge is largely through symbolic pathways and hence more psychological in type.

A deeper level type of attack, still psychological, is seen in the so-called “affect epilepsies” emphasized by Bratz. The patients are unable to adapt to intolerable curtailment in their energy distribution, no adjustment seems possible, and they go into a violent series of motor outbursts, clinically indistinguishable from more classical epileptic attacks. Such are seen, for instance, in prisoners locked up for a long term imprisonment and in soldiers in the Great War unable to get out of an intolerable situation. The wild outbursts of these patients may be accompanied by hallucinations, there is usually complete amnesia, and consciousness is frequently clouded, although not absolutely.

In the classical epileptic attacks the far-reaching disorganization of the energy distribution is seen in the complete loss of consciousness and the still further breaking up of all purposeful or adaptive movements. There is absolute destruction of all adaptations. Destruction is the motto of the nervous system, the channeling of nervous discharge, which Cajal has so beautifully illustrated, whereby the intensity of the energy may be evenly distributed (avalanche action), fails and total anarchy is the result. The attack involves not only the psychological, the sensorimotor but the physicochemical as well, as seen in the toxicity of the secretions, the alterations in liver metabolism, changes in blood coagulability, in adrenalin content, etc., etc. These changes are not the causes, as is so frequently urged by this or that student; they are the result.

As the patient comes out of his attack it may be seen to what low instinctive levels he has been reduced. He shows marked infantile breathing (abdominal type), he makes characteristic sucking movements of the mouth. He at first aimlessly fumbles about and slowly finds himself. Expressed in another way, he recapitulates the series of years of his growing up from childhood to an adult in the few minutes or hours that he takes to rerelease himself to his surroundings.

This comparison with the infantile life casts a light upon the unconscious processes which are going on in the epileptic attack. In this period of infancy it is known how wish-fulfillment by incoördinate movements is perfectly normal. The repressed or thwarted child will cry out, will

thrash and stamp and throw himself on the floor, will scream, lose his breath in anger, even become blue. These phenomena are lightly referred to as "fits of temper." Such a child will later throw things on the floor, kick the chairs, tear up his books, spit in one's face, while adults will go through similar mechanisms when they stamp the floor, clench their fists, grit their teeth, swear and show reactions of anger which are quite uncalculated to effect any real change in the conditions surrounding them. The meaning in all of these phenomena is the inability or lack of desire to accept, i.e., to adjust. These individuals are determined that a thing is not so because it cannot be so, that is, they do not wish it to be so. They make a supreme effort to change realities by thinking them different, which, because it fails, forces the energy discharge off into avenues, which cause a flight from the whole affair by rigidity and unconsciousness.

To understand the epileptic attack then it becomes imperative to study it from the top down, rather than from the bottom up; from the psychical towards the chemical, rather than the reverse. The first thing to understand is the "psychical defect" side of the problem. The faulty adjustments to reality must be understood from the highest of man's wishes, especially his greatest need, namely, social integration—social conformity. Dynamic psychology has made it an issue that all mental symptoms must have a teleological function. The epileptic attack as well as the epileptic deterioration must be viewed as responding to a need or wish of the patient. His first great defect is his faulty handling of the Œdipus function.

Socially speaking the epileptic tends to belong in a group by himself. His unconscious wish to differ utterly from all others is not sufficiently sublimated, or possibly capable of sublimation because of gross anatomical defect. Studies on the epileptic constitution by psychoanalytic methods have been unanimous in showing the antisocial attitude of the inner trends of the epileptic (Macder, Clark, Jelliffe, MacCurdy, and others). They cannot recognize, by adequate return, the protection which is offered by the social group. They remain selfish children, expecting everything and giving little or nothing. As MacCurdy well puts it, "The epileptic is therefore one born to trouble and bound to hate the world that means trouble to him." In his deterioration he retires from the world, gets to feel that he must be looked after, as he was when a child, and gives little or nothing in return.

Clark has shown a similar situation for the epileptic attack. It usually has its psychical setting. When things are going badly, when the patient is encountering difficulties, when he gets into conflicts and the world is not treating him as well as it ought, then the attacks come on. Again it is a flight from reality, but a flight with all the violent wish of the infant for omnipotence.

When one studies a huge number of attacks, as has been done in some of our epileptic institutions (Clark, 175,000 at Craig Colony), at least

two pertinent facts come out relative to ordinary factors of energy distribution. In the first place it is noted that on rainy days, holidays and Sundays the attacks augment. The patients are not busy. The more adequate energy adjustments of the usual routine of life are lessened, or shut off, and their false application is rendered easier. Again the curve goes up at the cessation of the day—at the beginning of the sleep hour. This too is the time of maximum struggle between reality and phantasy.

The epileptic, let his nervous pathways be impeded by what may, a tumor, a scar, a failure of development, a toxemia or any of the two or three hundred different brain lesions which are known to accompany the epileptic attack, is an epileptic, partly by reason of this handicap, which may be non-recognizable or quite apparent, but also partly because he has not learned to wish to conform to those ideas about him which work for the advance of the social body. Recent studies by MacCurdy, Jelliffe, Maeder, and Clark have shown this most abundantly. MacCurdy aptly says of the epileptic—he is speaking of the essential epileptic, or what in this article would be termed the epileptic whose organic handicap is minimal or difficult of recognition: “. . . when he lets his adaptations go, loses more than what these adaptations gave him. This tendency—that it may progress further in the patient than in the average man—is no stranger to any of us. We all have traces of the epileptic reaction when we give way to temper, choose the easier path, or allow our egoism to sway our judgment. In so far as we have these characteristics, we are liable to the fate of these victims of self. It is ordinarily supposed that the egoist loses only the regard of his fellows when he obtrudes his egoism. But if psychoanalytic studies in epilepsy have no other value, they would be justified in the demonstration they give of the fate of the egoist who loses his mental capacity as fast as he loses contact with the world. The egoist is relentlessly pursued by the nemesis of intellectual degradation. Born social, not solitary beings, our mental capacity seems dependent on our retaining a vital interest in our fellows. The bonds that unite all human beings are not merely essential to the species, they are an integral part of the individual. These lost, the personality, even mentality is lost. To put the matter in lay terms, we must love, not merely be loved; we are under compunction to love or cease to be ourselves, cease even to think.” An ancient Greek philosopher said it in another way. “We think alike,” said Protagoras, “concerning those things which are necessary to live; we vary concerning those things which are not needed for a bare existence, though they may conduce to a life that is beautiful and good; but it is only when we do not act at all that we can differ utterly from all others and live our own lives apart.” The epileptic is hindered from action, by his fit, because he wants to differ utterly from all others.

Line 28-30 *read:*

With this **simple** symptom review, especially of the mental features,

with the etiological possibilities and with a brief résumé of the dynamic significance of the attack in view, one is ready to start on the therapeutic problems involved.

646. Lines 37-42 *substitute*:

Psychotherapy.—While common sense will go a long way in adjusting many of the mental difficulties of the average genuine epileptic, it will not suffice. These patients are epileptic as a result of a special way they have found to handle their unconscious conflicts. These epileptics need a psychoanalysis and it may be said that nearly all epileptics—even the most organic types—would benefit if they could obtain a deeper insight into the activities of their unconscious.

648. Line 37 *add* after “nothing.”:

The gastro-intestinal surgical treatment of epilepsy is also nonsense, if used as a routine procedure.

650. Lines 4-10 (B. F.). Lines 1-7 (F.) *read*:

19. Freud, S. *Die Psychopathologie der Alltagsleben*, 2. Aufl., Berlin, 1909. *Die Traumdeutung*, 2. Aufl., etc., etc. See especially the collected review with bibliography, by E. Hitschmann, *Freud's Neurosculare*, Leipzig u. Wien, 1911. **Theories of the Neuroses. Nervous and Mental Diseases Monograph No. 17.** Some of Freud's works are translated into English. *Nervous and Mental Disease Monograph Series*, New York.

20. ——. **Three Contributions to the Theory of Sex. Nervous and Mental Disease Monograph Series 7, 2nd Edition, 1916.**

651. Lines 15-16 (B. F.). Lines 9-10 (F.) *read*:

1. Déjerine and Gauckler. *The Psychoneuroses*, Translated by Dr. Smith Ely Jelliffe, Lippincott.
2. Jelliffe. *Hysteria*, *Mod. Med.*, vii.

Add under “HYSTERIA”:

Freud. *Hysteria*, *Nervous and Mental Disease Monograph*, No. 4.

Add under “EPILEPSIES”:

Jelliffe and White. *Diseases of the Nervous System*. Chapter on the Epilepsies.

VOLUME V

CHAPTER I

THE PRINCIPLES OF SPECIFIC THERAPY

ERNEST E. IRONS

17. Line 14 *add* after "toxic.":

Other writers, following the lines suggested by the work of Bordet, have found that by mixing serum with kaolin substances are produced equally as toxic as those derived from mixtures of serum and bacteria, and from these experiments have argued that the toxic substance is probably derived from proteolysis of the serum itself rather than from the bacteria.

30. Lines 27-30 *read*:

suppurative focus, such as may be found in tonsils, **sinuses, alveolar abscess or gall-bladder**, call first for surgical treatment of the primary lesions, **and when the focus of infection is removed the natural resistance of the body is usually sufficient to overcome the remaining infection.**

37. Line 4 *add* after "serum.":

Gay and others have used sensitized typhoid vaccine extensively for both immunization and treatment (*see* Typhoid Fever).

Line 30 *add* after "procedure.":

TREATMENT BY INTRAVENOUS INJECTIONS OF FOREIGN PROTEIN

The treatment of disease by intravenous injections of homologous and of foreign proteins including those of bacterial origin has recently occupied the attention of both the laboratory and the clinic, and the physician is confronted by the question as to how far he shall utilize these methods in the treatment of patients in his charge. The answer to this query is difficult. Two questions seem to be involved: one, as to what extent the phenomena of the reaction are part of the mechanism of the recovery from

disease; the other as to whether, in the present state of our knowledge, practical results justify the use of the method in the treatment of patients.

In brief, the phenomena which follow the intravenous injection of bacterial protein or of albumose are a rise in temperature with rigor, and more or less profound general symptoms such as rapid pulse, cyanosis and marked increase in leukocytosis, followed by a drop in temperature. Changes in serologic reactions with respect to opsonins or agglutinins have been noted. When such reaction is provoked in persons suffering from typhoid or other febrile disease the fall in temperature may be permanent, as in the crisis of pneumonia, and convalescence seems in certain cases to be hastened.

Typhoid fever, puerperal sepsis, pneumonia, erysipelas, arthritis of various forms, are some of the diseases which have been treated in considerable numbers by this method.

Before considering some of the questions of therapeutics which are suggested in these interesting reactions, it is desirable to point out in what respects they promise to modify the hitherto accepted views of immunity.

Specificity in biologic reactions has been the guiding principle of those who have attempted to devise methods of therapy in infectious diseases. The theory of antigen and antibody, developed by the genius of Ehrlich, has dominated therapeutic research in infectious disease up to the present time. His conceptions of strict specificity in the relation of the reaction products of the animal body to foreign protein, whether of bacterial or other origin, have been repeatedly questioned, but while his theories have required modifications to meet the requirements of the physicochemical principles, the fact remains that it has been under their guidance that our most valuable specific remedies, such as antisera for diphtheria, tetanus, and meningitis, salvarsan, prophylactic immunization against typhoid, and diagnostic aids based on agglutinins, precipitins, and complement fixing substances, have been developed.

In considering the possible non-specific elements in the phenomena of disease, it is not proposed therefore to supplant the older specific conception, but to discover in what ways these non-specific reactions help or hinder the specific factors, or act independently of them.

It is also important to bear in mind that the specific biologic reactions which present so high a grade of specificity that we have come to regard them as something apart from ordinary chemical reactions, are merely instances of physicochemical processes, whose fine degree of adjustment can be attained only under conditions met with in the animal body. The phenomena of agglutination, phagocytosis, and precipitation, can all be produced artificially—though less perfectly than by using materials from the animal body—by properly adjusting and modifying the concentration of electrolytes, or the surface tension of nonmiscible fluids.

And so no matter what the ultimate conclusion as to the nature of the nonspecific reactions may be, it is altogether probable that they follow the same chemicophysical laws as reactions which we have come to regard as highly specific.

The first question we may ask is: In the course of and recovery from infectious disease, to what degree are specific and nonspecific factors concerned?

In typhoid fever the specific factors so far as we know them seem to be opsonins, lysins, and from recent studies also the agglutinins.

Of the nonspecific factors in the production of the symptomatology of typhoid we note that Vaughan years ago suggested that the fever of typhoid was caused by products of splitting of typhoid protein, and he was able to produce various types of fever in animals by the injection of protein split products obtained by hydrolyzing bacterial protein of colon or other bacteria, or egg white. Phagocytosis, both endothelial and leukocytic, seems to be important. Polynuclear phagocytosis is facilitated by specific opsonins, and Gay has maintained that the hyperleukocytosis following intravenous injections of typhoid bacilli is also specific in that it is more pronounced in animals previously immunized than in non-immunized animals. Other investigators have failed to confirm Gay's work in this respect, and find that the hyperleukocytosis is nonspecific and can be elicited in untreated as well as in treated animals. The phenomena of the reaction are not peculiar to patients suffering from febrile disease, for the same reaction has been observed in normal persons injected intravenously with typhoid vaccine.

Several theories have been advanced to explain the change in the clinical picture and disappearance of previous symptoms of disease following intravenous injections.

Jobling and Petersen have shown that the serum protease of the blood is increased by intravenous injection of protein, and suggest that the ferment normally held in check by antiferment is freed by the removal of the latter, and at once acts on the toxic fever—producing substances in the body, breaking them down to nontoxic elements.

The hyperleukocytosis which accompanies the reaction has also been held to accelerate the phagocytic removal of invading bacteria. This seems to be largely a nonspecific factor.

There is also some evidence to indicate that the reaction produces indirectly a specific effect by mobilizing or calling into action specific immune substances which have already been formed, but have not developed their maximum effect in the body of the patient.

Perhaps the most important question to all is—To what extent may those nonspecific methods be at present employed in therapeutics with profit and at the same time safety to the patient?

It must be evident that our knowledge of what takes place in the body

of the patient is at present largely conjectural. Clinically, on the one hand we have reports of rapid defervescence and apparent improvement in some of the cases of typhoid, and of subsidence of arthritic phenomena in patients suffering from infectious arthritis, following the intravenous injection of foreign protein. On the other hand, many patients derive no demonstrable benefit, and in still others the improvement noted is ascribable to the natural course of the disease as well as to the treatment. Nor can we overlook the severe reactions, the instances of cardiac dilatation, and also the occasional though rare deaths which have at least followed, if they have not been due to the injections.

The study of the nonspecific phenomena of disease is of great importance, perhaps greater than we now realize, and promises to open for us new avenues of attack by which we may hope to arrive at a better understanding of the way in which recovery from infectious disease occurs.

It is possible too that methods may be found to obtain the favorable nonspecific effects without exposing the patient to the rigorous experiences of present methods.

From the point of view of safe therapeutics, however, it would seem well for the present to maintain great conservatism in employing these methods in the treatment of the disease even under circumstances which permit of careful study and control. Their general and indiscriminate use is to be condemned.

The balance of immunity is a very delicate one, which may easily be deflected for or against the patient, and we shall not wish to alter this balance unless we can be sure that the change will be uniformly in favor of the patient.

CHAPTER II

THE FUNCTIONAL ANALYSIS OF ANAPHYLAXIS

JOHN AUER

39. Lines 3-5 *read*:

laxis, or protein hypersensitiveness **and on its basis insight has been gained into many puzzling processes, especially in the so-called idiosyncrasies.** Any living structure of the organism apparently may be the

43. Line 11 *add* footnote after "mates.¹":

¹That important changes in the liver occur after simple sensitization has been noted in the guinea pig by Hashimoto and Pick; these changes, however, bear no direct relationship to the anaphylactic reaction.

45. Lines 42-44 *read*:

and dried or fresh horse flesh (Rosenau and Anderson, 100); **or by feeding raw cow's milk (Kleinschmidt); or perhaps even** by the *instillation* of one drop of normal horse serum into the intact conjunctival sac (Rosenau and Anderson, 101), **though this has not been corroborated by Colombo.**

47. Line 3 *read*:

injecting an extract of the lens of the other eye (Uhlenhuth and Handel. **See also Romer and Gebb, and Kapsenberg.)**

48. Line 20 *read*:

tive during life, which is about 3 years; **the degree of sensitization, however is considerably decreased after 3 years, so that 5-10 times the original lethal dose is then merely toxic and does not kill (Auer, 9).** In human beings typical anaphy-

Line 27 *read*:

months, after a single sensitizing dose of horse serum; **in one surviving dog Auer (9) obtained the typical blood pressure effect one year after sensitization.**

49. Line 10 *read*:

majority of cases, **though respiratory and circulatory changes also occur.** A fairly detailed description of the symptoms and

50. Line 26 *read*:

In the intervals between convulsions the animal lies motionless **on its side**; the legs

58. Line 32 *read*:

blood in the **left ventricle** many inches into the air. Failure or

60. Line 24 *read*:

bronchomotor effect of vagus stimulation, it seemed legitimate to attribute

62. Line 29 *add* after "lungs.":

It must be observed that Schultz and Jordan's work does not entirely explain the distention of the anaphylactic lung, for small pieces of the lung cut from the periphery of the lobes do not collapse. It is possible that this is due to an increase in the rigidity of the tissue elements.

77. Line 30 *read*:

and guinea-pigs. To this group the writer would also add **on the basis of his experiments** the blood-

80. Line 10 *read*:

central tendon of the diaphragm (**Auer, 9**). It is **probable** that these beadings play a

82. Line 13 *read*:

able within one hour as a rule (**Auer, 9**).

87. Line 8 *add* after "animal.":

Some remarkable liver alterations have been noted by Hashimoto and Pick; these authors describe a doubling or even trebling of the non-coagulable nitrogen in the guinea-pig's liver after mere sensitization by horse serum; they also observed that the livers of the same species obtained after acute anaphylactic death show only slight or no post mortem autolysis.

90. Line 14 *add* after "eosinophiles.":

In passive anaphylaxis no eosinophilia is observed. There is no relation between the degree of anaphylactic reaction and the degree of eosinophilia.

112. Line 17 *add* after "947-1154.":

Also by the same author—Neuere Ergebnisse d. Anaphylaxiforschung in Ergebnisse d. Immunitätsforschung, Exp. Therap., Bakt. u. Hyg., 1914, I, 257.

Add under "References.":

Colombo, G. L. Tentative di antianafilassi mediante instillazione nel sacco congiuntivale, Ann. di ottalmolog., 1913, XLII, 711.

Hashimoto, M., and Pick, E. P. Ueber den intravitale Eiweissabbau in des Leber sensibilisierter Tiere und dessen Beeinflussung durch die Milz, Arch. f. exp. Pathol. u. Pharm.

- v. Heinrich, H. Der anaphylaktische Schock nach Bestrahlung des sensibilisierten Tieres, Zentralbl. f. Bakt., 1913, LXX, 421.
- Kapsenberg, G. Die Anaphylaxie mit Linsensubstanz, Zeitschr. f. Immunitätsforsch., 1912, XIII, 518.
- Kleinschmidt, H. Ueber Milchanaphylaxie, Monatsschr. f. Kinderheilk. (Orig.), 1913, XI. See also Vert. d. 29ten Vers. d. Gesellschaft f. Kinderheilk., Münster, 1912.
- Romer, P., and Gebb, H. Weiterer Beitrag zur Frage der Anaphylaxie durch Linseneiweiss, Graefe's Arch. f. Ophth., 1913, LXXXIV, 183.
- Weinberg, M., et Seguin. Anaphylaxie et eosinophilie, Compt. rend. Soc. Biol., 1914, LXXVI, 585.
- Add to "Reference 128."*:
- . Ergebnisse d. Immunitätsforsch., 1914, I, 372.

CHAPTER III

IMMUNOLOGICAL REACTIONS IN DIAGNOSIS

GEORGE F. DICK

124. Lines 20-21 *read*:

rods, **about 0.5 to 0.8 μ in breadth and 1 to 3 μ in length.** The typhoid bacillus does not form gas in dextrose media, does not form acid in **lactose and** saccharose, but does form acid in milk and in mannite. Indol

Line 41 *add* after "serum.":

Gay and Claypole state that two transplantations on 10 per cent. rabbit's blood agar rendered typhoid bacilli nonagglutinable in an immune serum produced with plain agar cultures. This is not borne out by the work of Bull and Pritchett.

131. Line 35 *read*:

been described. **Craig has called attention to the necessity of maintaining the sterility of the serum to be tested, as the action of bacteria on the serum influences the outcome of the test.** It is well to provide about 2 c.c. of serum in order to

132. Lines 40-41 *read*:

preparations two have been found especially valuable.

1. Acetone insoluble extract of heart. Noguchi gives the following method of preparation.

133. Line 9 *add* after "test.":

2. Cholesterinized antigens, advocated by Sachs, McIntosh and Fildes and Walker and Swift. Walker and Swift recommend the following procedure for the preparation of cholesterinized alcoholic extract of the human heart. "The tissue free from fat was minced, weighed and placed in absolute alcohol in the proportion of one gram of tissue to 10 c.c. of alcohol. Extraction was carried on in the incubator at 37° C. for two to three weeks. The bottle was shaken daily. The extract was cooled to room temperature and filtered. The filtrate was used as a stock solution. To this stock solution 0.4 per cent. of cholesterin was added."

We have found it well to use both these antigens as a routine. Most

observers have found the cholesterinized alcoholic extract to be more sensitive but to give a higher per cent. of positive reactions in cases in which the probability of syphilis is slight.

136. Lines 10-31 *substitute*:

WASSERMANN SYSTEM WITH HEATED SERUM

A series of seven test tubes is arranged in a rack, and into each is measured 0.5 c.c. of complement. Into No. 1 are put 0.1 c.c. of serum to be tested and 4 units of antigen. Tube 2 is made up as tube 1, except that the antigen is omitted. Tube 3 differs from tube 1 in that 0.1 c.c. of known positive serum is used instead of the test serum. Tube 4 is as 3, but without antigen. Tube 5 contains the same reagents as 3, excepting that either 0.1 c.c. of salt solution or 0.1 c.c. of normal serum is added, instead of positive serum. Tube 6 is as tube 5, excepting that it is without antigen. Into tube 7 are put 0.5 c.c. of heated suspected serum and 0.5 c.c. of sheep's corpuscle suspension. Tube 8 is the same as 7, excepting that it has 0.1 c.c. of suspected serum instead of 0.5 c.c. Tube 9 may be used for a second antigen (see page 133). The tubes are now all made up to 1.5 c.c. and incubated for 1 hour at 37° C. At the end of that time 0.5 c.c. of corpuscle suspension and 2 units of amboceptor made up to 0.5 c.c. are added. In the event that complete hemolysis has occurred in tube 7 the amboceptor is omitted from 1 and 2. If complete hemolysis has not taken place in 7 but has in 8 one unit of amboceptor is added to 1 and 2. The tubes are now incubated for an hour and again observed. In case the test is positive the opaque corpuscle suspension will be unaffected. If it is negative there will be hemolysis. The controls should be as follows: Tubes 2, 4, and 6 should be hemolyzed, as there should be no fixation of complement without antigen. Tube 3 should show no hemolysis, as there should be fixation of complement with the syphilitic serum. Tube 5 should be hemolyzed as the antigen alone, or with negative serum, should not fix complement.

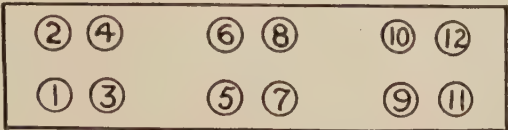


FIG. 2.—ARRANGEMENT OF TEST TUBES FOR THE WASSERMANN REACTION.

137. Line 6 *add* after "heated.":

Hauptmann and Hossli use graded amounts of spinal fluid up to a maximum of 1 c.c. in a total volume of 3 c.c. McIntosh and Fildes consider it very doubtful if quantities over 0.4 c.c. in 2 c.c. are of value.

138. Line 28 *read*:

let fever, leprosy, tuberculosis, carcinoma, jaundice, and diabetes in which positive

139. Lines 4-7 *read*:

somiasis in this country makes confusion in diagnosis unlikely. **It has been shown that the positive reactions obtained in scarlet fever were at least in part due to the use of poor antigens and that a positive reaction occurring in scarlet fever is suggestive of syphilis.** The positive reactions in carcinoma, tuberculosis, and diabetes

142. Line 30 *add* after "it.":

Recently Warden and Schmidt have advocated an absolute alcohol extract of gonococci as an antigen giving a higher per cent. of positive tests than other antigens.

The employment of lipid antigens in other diseases has met with the difficulty of positive reactions in syphilis (*see* page 145). Kolmer has found the alcoholic extracts of little value, the best results being obtained with simple aqueous suspensions.

144. Line 30 *add* after "discharge.":

Kolmer states that 60 per cent. of all gonorrheal cases give positive tests. The highest per cent. (83 per cent.) of positive tests is obtained in gonorrheal arthritis.

145. Line 23 *add* after "writers.":

Some of these have advocated the reaction as a valuable means of diagnosis. There have been many different methods of antigen preparation and there seems little doubt that specific reactions are obtainable by some of these methods. (*See résumé* by Korper.) One difficulty with this and other immune reactions in tuberculosis is well stated by Hanman, who reminds us that the prevalence of tuberculous infection makes it necessary for the clinician to distinguish between the presence of tuberculous infection and tuberculous disease, a distinction which in other diseases, as syphilis, is not necessary.

148. Line 44 *add* after "widely.":

The thorough quantitative work of Van Slyke, Vinograd, Wilchur and Losee has shown that although the serum of pregnant individuals averages higher in proteolytic power than that of nonpregnant individuals, the range of proteolytic power of pregnant and nonpregnant sera is so nearly alike that the test is of little practical value.

149. Line 24 *add* after "controls.":

The results of Dick, Van Slyke, and others indicate that the test is of little value.

155. Line 21 *add* after "diagnosis.":

Accordingly as the patient is immunized against a preformed toxin or merely sensitized to a substance not in itself a toxin, there are two types of allergic reactions occurring in the body of the patient:

1. In which preformed toxin is used as antigen,—a positive reaction

indicates a lack of immune substances. The Schick reaction is the only test of this type in use and as it is not strictly a diagnostic test it is discussed elsewhere.

2. Reactions in which the nontoxic antigen must be converted into toxin by anaphylactic antibodies. It is this type of reaction which has been of most value in diagnosis.

161. Line 31 *add* after "test.":

Holmes has used the intracutaneous test quantitatively; the tuberculin, injected in quantities of from 1/100 mg. to 1/100,000 mg. dissolved in the constant amount of 1/20 c.c. of diluent (salt sol. with 0.5 per cent. of carbolic acid added), was used. The reaction was at its height in 48 hours, while the control reaction had subsided by this time. The positive reaction was characterized by an area of hyperemia $\frac{3}{4}$ to $2\frac{3}{4}$ cm. in diameter. In this way the degree of hypersensitiveness in the different stages of the disease was ascertained. During the onset of the infection the hypersensitiveness was marked. It diminished with improvement; fluctuated or remained stationary with nonimprovement.

164. Line 12 *read*:

limate solution and 0.07 c.c. (one drop) of a **1:1 dilution in salt solution** of the antigen injected intracu-

166. Line 3 *add* after "Reaction.":

The reaction is positive in almost all cases irrespective of syphilis if obtained before, during or shortly after the administration of iodids, as shown by Sherrick.

Line 8 *read*:

In a study of a variety of cases Wolfsohn **and more recently Hanes** came to similar conclusions.

Add under "References.":

Bull and Pritchett. Jour. Exp. Med., 1916, XXIV, 35.

Craig. Jour. Exp. Med., 1911, XIII, 521.

Dick. Jour. Infect. Dis., 1914, XIV, 242.

— and Dick. Jour. Infect. Dis., 1916.

Gay and Claypole. Arch. Int. Med., 1913, XII, 621.

Hamman. Bull. J. H. Hosp., 1915, XXVI, 276.

Hanes. Am. Jour. Med. Sci., 1915, CL, 705.

Hauptmann and Hossli. Münch. med. Woch., 1910, 1581.

Holmes. Bull. Johns Hopkins Hosp., 1915, XXVI, 12.

Kolmer. Jour. Infect. Dis., 1914, XV, 6.

Korper. Trans. Chi. Path. Soc., 1916, X, 62.

McIntosh and Fildes. Brain, 1913, XXXVI, 193.

McIntosh and Fildes. Ztschr. f. Chemother. Orig., 1912, I, 79.

Sachs. Berl. klin. Woch., 1911, XLVIII, 2066.

Sherrick. Jour. A. M. A., 1915, LXV, 404.

Van Slyke, Vinograd, Wilchur and Losee. Jour. Bio-chem., 1915, XXIII, 377.

Walker and Swift. Int. Exp. Med., 1913, XVIII, 75.

Warden and Schmidt. Jour. Lab. and Clin. Med., 1916, I, 333.

CHAPTER V

THE PROPHYLAXIS OF TYPHOID FEVER BY MEANS OF VACCINES

FREDERICK F. RUSSELL

201. Line 28 *add* after "small-pox.":

[The military experience of the past two years has tended to confirm the conclusions derived from army and hospital statistics during times of peace, concerning the value of antityphoid vaccination as a protective measure against typhoid fever. It has been urged by some that the elimination of typhoid fever from our army following the introduction of antityphoid vaccination was due not so much to vaccination as to improved sanitary conditions. This argument will hardly hold, however, in view of the success in controlling typhoid under the severe conditions of trench warfare on the western front in Europe.

TYPHOID AND PARATYPHOID.—Vaccination against typhoid fever does not seem to protect against infections caused by paratyphoid organisms. During the early months of mobilization in the present war, certain troops were immunized against typhoid only. When these troops entered the field a few months later, typhoid fever was almost entirely absent, but paratyphoid was found in a number of instances. Subsequently paratyphoid vaccine was included with the typhoid for immunization.

Paratyphoid infections are not so common as typhoid, but since the circumstances of infection are similar in these diseases, it is advisable to include paratyphoid A and B with the typhoid organisms in the immunizing vaccine.

Dosage.—The first dose of vaccine may contain 500 millions of killed typhoid bacilli, 250 millions of paratyphoid A and 250 millions of paratyphoid B. The second and third doses are each double the amount of the first injection, that is, 1,000 millions of typhoid and 500 millions each of paratyphoid A and paratyphoid B. The reactions following the vaccine containing paratyphoid in addition to the typhoid bacilli do not appear to be more severe than those following immunization by typhoid bacilli alone.—Editors.]

CHAPTER VI

BACTERIAL AND SERUM THERAPY IN TYPHOID AND PARATYPHOID FEVERS

WILLARD J. STONE

222. Line 33 *add* after "death.":

The intravenous administration of the ordinary nonsensitized vaccine is certainly not without an element of danger and is not to be recommended.

223. Line 6 *read*:

Sensitized Vaccine Therapy.—The recent adoption by many clinicians of the sensitized vaccine of

Line 23 *read*:

through the use of sensitized vaccine if used early in the course of the fever. Gay and Chickering have recently reported the most encouraging results so far obtained. They have used a sensitized polyvalent killed vaccine sediment prepared after the method of Gay and Claypole. The dosage used by them varied from 1/50 to 1/_5 mg. of the dried sensitized vaccine intravenously, which they have found corresponded to a dose of 150 to 300 million bacteria. In sixty-five cases a distinct benefit was obtained in 66 per cent., in over half of whom the recovery was of an abortive type with a critical fall of temperature and the establishment within a few days of a permanent normal temperature. This permanent normal temperature was reached on an average seven days after beginning treatment. The sensitized vaccine sediment produces but slight reaction as compared with the nonsensitized vaccines heretofore used intravenously. The dose may be repeated every two or three days, depending upon the clinical signs of reaction. The vaccine probably acts as a marked stimulant to phagocytosis. A series of subcutaneous injections is recommended by Gay and Chickering following the intravenous treatment as an aid in the prevention of relapses.

232. Add to "Reference 49.":

Arch. Int. Med., 1914, XIV, 67.

Gay, F. P., and Chickering, H. T. Arch. Int. Med., 1916, XVII, No. 2.

CHAPTER VII

BACTERIAL THERAPY IN LESIONS PRODUCED BY THE BACILLUS COLI COMMUNIS

WILLARD J. STONE

251. Line 7 *add* after “(Chapter VI).”:

Vaccines sensitized by the addition of an immune serum and subsequently killed produce less constitutional reaction when injected and should be preferred for intravenous administration if such a method is selected. The immunity produced has not, however, in my experience, been greater than that produced by the ordinary nonsensitized vaccine. Much more rapid absorption of the vaccine occurs after an intramuscular injection than occurs after a subcutaneous injection and should usually be the method of choice. The injection of living sensitized vaccines at the present time does not appear warranted.

CHAPTER XI

WHOOPING-COUGH (PERTUSSIS)

E. MATHER SILL

302. Line 9 *add* after "indefinite.":

Povitsky in a study of the agglutination in 59 pertussis cases has shown that a strongly agglutinating serum is best obtained in the rabbit by 10 or 12 intraperitoneal inoculations of living culture given at several day intervals. Over 95 per cent. inoculated in this manner produced agglutinins.

A high-titer serum (1:4000 to 1:10,000) was always a quickly acting serum, while a low-titer serum was slow in reaction. *Bacillus pertussis* strains can be specifically identified by agglutination tests from hemoglobinophilic bacilli, pertussis-like bacilli, and *Bacillus bronchisepticus*. Cross agglutination between these organisms did not occur higher than 1:40.

A strong serum agglutinates all pertussis strains equally well, but not equally promptly in the highest dilutions (1:2000-2500).

For a positive diagnosis by the agglutination test a dilution of 1:200 is necessary, since out of 51 controls about 33 per cent. of nonpertussis adult sera showed agglutination in up to 1:40; 17 per cent. in up to 1:100. Forty per cent. control children's sera (scarlet fever cases) agglutinated in up to 1:40.

This test compares favorably with the complement fixation test only in the first week of the whoop. In later stages complement fixation antibodies are more frequent than agglutinins.

Olmstead and Luttinger made complement fixation tests on serum from 111 cases of pertussis and suspected pertussis, and about 40 per cent. gave a positive reaction with antigens of the Bordet-Gengou bacillus when an active serum was used. Convalescent vaccination cases have shown the highest per cent. of positives.

304. Line 34 *add* after "weeks.":

Further experience with the use of pertussis vaccine has shown that much

larger doses can be given with perfect safety, and with such rapidly ascending doses a quick amelioration of symptoms may be confidently expected.

Line 37 *read*:

doses of **100,000,000 to 200,000,000 and doubled** every two to three days, according to the age

305. Lines 20-30 *substitute*:

Luttinger (6), who has treated a large number of cases with pertussis vaccine in the Department of Health whooping cough clinics in New York, has been using much larger doses with apparently better results and no untoward effects. (Rarely more than three injections were given.) His initial dose is 250 million bacteria, which is doubled every other day, provided there is no reaction. That is, the second dose is 500 million, the third one billion, and the fourth two billion. In nearly 3000 injections given he has never seen a severe reaction as evidenced by temperature of 103° to 100° F., accompanied by malaise or vomiting, diarrhea and chills. My more recent experience in giving approximately the same large doses of the specific vaccine as put up by the New York Bureau of Laboratories would seem to corroborate his observations. Of 138 cases which were treated by Luttinger with vaccines, 115 were seen during the first three weeks of the paroxysmal stage, and their average duration was 25 days; while the average duration of 35 similar cases treated with drugs (antipyrin and sodium bromid) was 40 days.

308. Lines 1-31 *substitute*:

The effect of the vaccine treatment on a case of pertussis is first a decrease in the severity of night paroxysms, then vomiting usually stops, and the day paroxysms become less severe. This is followed after a few days by absence of night paroxysms and a reduction in the number of day paroxysms, so that by the end of a week or ten days the number of whoops is reduced to about a quarter of their previous frequency.

Preparation of Vaccine

The Bureau of Laboratories of the Health Department prepares the vaccine as follows:

A 48-hour culture on the special Bordet-Gengou medium is scraped off with normal salt solution, shaken three or four hours in the shaking apparatus, and heated for an hour to 60° C. (or left in an incubator over night at 56° C.) and standardized according to the Wright method, 0.25 per cent. carbolic acid being added as a preservative.

309. Line 29 *read*:

Hess reports the prophylactic inoculation of 244 children in the Hebrew Infant Asylum, where there was an epidemic of pertussis. Of

these, 20 developed the disease in from two and a half weeks to two and a half months or more, or one in twelve developed the disease; while of 80 children who were not vaccinated 59, or nearly three in four, developed whooping cough. When a child is

310. Line 31 *add* after "per cent.":

In 1915, 6,868 cases were reported in New York, with 385 deaths, or a mortality of 5.60 per cent. When consideration is taken of unreported, atypical and adult cases the mortality is probably about one per cent. for the disease, all ages included.

312. *Add* under "References.":

Hess, Alfred F. Jour. A. M. A., Sept. 19, 1914, Vol. LXIII, p. 1007.
Olmstead, Merian, and Luttinger, Paul. Arch. Int. Med., July, 1915,
Vol. XVI, pp. 67-85.

Povitsky, Olga R., Col. Stud. Bur. of Lab., N. Y. City Health Dept.,
Vol. VIII, 1914-15.

CHAPTER XIV

SPECIFIC TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

HOMER F. SWIFT AND CAPT. ARTHUR W. M. ELLIS

408. Line 22 *read*:

complement in the Wassermann reaction; **(4) type of curve given by the Lange Gold Reaction.** In addition, it is well to note

Line 33 *read*:

examination of the other **four** constituents is very important, and none of

410. Line 25 *read*:

use of **ten** volumes of fluid, as compared with one volume of blood serum,

Line 28 *add* after "present.":

For the past four years we have been testing the fluid in amounts corresponding to 2 c.c. and have occasionally detected positive reactions in this quantity when lower dilutions gave negative reactions.

411. Line 21 *add* after "syphilis.":

LANGE GOLD REACTION.—This test requires for its performance a proper solution of colloidal gold, which is red in color. The spinal fluid is diluted with 0.4 per cent. NaCl as follows: 1-10, 1-20, 1-40, 1-80, 1-160, 1-320, 1-640, 1-1280, 1-2560, 1-5120. Then the colloidal gold solution is added, well shaken and allowed to stand over night, after which the readings are made. With abnormal fluids the red color in certain of the tubes is changed. These changes are designated by numbers; i.e., 1 red-blue, 2 lilac or purple, 3 blue, 4 pale blue, 5 colorless. Thus the reading 5555421000 indicates that the first four dilutions were completely decolorized, the fifth dilution pale blue, the sixth lilac or purple, the seventh red-blue and the next three unaffected. This is the typical paretic curve in which the first four to six or more tubes show discoloration. In the luetic type of curve there is not a complete decolorization of the first dilution and the maximum change occurs in the second to the fourth or fifth tubes, i.e., 3334310000, or 1221000000.

The luetic type of curve given by the fluid in cerebrospinal lues and

tabes is of confirmatory value. Its great usefulness, however, seems to be in differentiating paralytic dementia from these two conditions. The fact that the fluid from a patient with a clinical diagnosis of tabes or cerebrospinal syphilis gives a paretic curve does not militate against it, for it is well known that between ten and fifteen per cent. of tabetics develop paresis, and at times it is with the greatest difficulty that the differential diagnosis between cerebral syphilis and paresis can be made. If future observations confirm what now seems most probable, viz., that these paretic curve findings in the spinal fluids of patients, clinically not paresis, point to a possible development of the disease, it will be of importance in prognosis and of value in determining why symptoms of mental disorder appear in spite of vigorous and prolonged treatment.

414. Line 34 *add* after "amounts.":

Because of these unpleasant symptoms which follow intraspinal injections of neosalvarsan most clinicians in this country have given up this mode of treatment. Gennerich still injects fractions of a milligram in very dilute solutions. This author has become so enthusiastic over the results of intraspinal injections of these small amounts that he recommends that every patient in whom there is positive evidence of cerebrospinal syphilis should be treated in this manner. With such recommendations we disagree because (1) we feel that intraspinal treatment is not necessary in every case and (2) salvarsanized serum can be administered with greater safety.

415. Line 14 *add* after "per c.c.":

Because of the uncertainty of the dose of salvarsan in autosalvarsanized serum, Ogilvie has recommended that a definite amount of salvarsan be added to serum. In his and Fordyce's studies it has been found that the injection of this artificially salvarsanized serum is followed by distinctly beneficial results. It was further found that the dose of added salvarsan must be kept below 1 mg., or symptoms of myelitis of the lower part of the cord would appear. The dose now recommended is from 0.1 to 0.5 mg. The chief advantages of this method are known dosage and ease of preparation of serum for several patients at one time. One of us (Swift) has recently demonstrated that the most markedly spirocheticidal serum was furnished by adding a small amount of salvarsan to the serum of a patient who had received an intravenous injection of salvarsan. Another substance which has been recommended by Byrnes is the albuminate of mercury. When the dose is kept below 1 mg. repeated injections of this drug are reported to have been followed by beneficial results. In the preparation of this substance only human serum should be used, for repeated injections of horse serum may lead to the serious condition of hypersensitiveness or anaphylaxis to the foreign protein.

Line 30 *add* after "treatment.":

The results of the treatment of paretics as far as permanent arrest or cure is concerned have been disappointing. There is no doubt that the number and length of remissions are much increased when a group of paretics is intensively treated. Many of these patients have been able to return to their work for prolonged periods after treatment had cleared up their abnormal mental symptoms. However, the disease shows a marked tendency to relapse and finally most of the paretics come to an unfortunate end. Some authors claim this is due to the failure of the serum injected intraspinally to reach the site of the active lesion in the cerebral cortex. For this reason intraventricular injections of dyes, such as trypan blue, into the lateral ventricles is followed by a more intense staining of the cerebral cortex than when they are injected intraspinally. While theoretically the intraventricular injections of serum may be advised, it is difficult to repeat such treatment as frequently and as often as intraspinal injections can be given. Dr. Cotton in a personal communication has informed us that practically no better results are obtained from intraventricular injections than from intraspinal. The failure to cure permanently a case of paresis should not interfere with the undertaking of treatment, for the return of a paretic to his business or family, even if only for a year or two, may be of extreme importance.

418. Line 3 *add* after "employed.":

If it is desired the serum may be injected without dilution with saline. In this case 15 to 20 c.c. of whole serum are injected.

Line 8 *add* after "essential.":

OGLIVIE METHOD.—Serum is obtained from either an untreated or treated patient in the same manner as above described. Ten c.c. is pipetted into a sterile tube and to it the requisite amount of a weakly alkaline salvarsan solution is added and well mixed. This serum-salvarsan mixture is then incubated for one hour at 37° and afterwards heated to 56° C. for one-half hour, when it is ready for injection.

MERCURIALIZED SERUM. BYRNES METHOD.—To 12 c.c. of serum is added 1 c.c. of a solution of mercuric chlorid in freshly distilled water, so made that each cubic centimeter contains 0.0013 gm. (1/50 grain) of mercuric chlorid. To the serum thus prepared is added a sufficient quantity of normal salt solution to make a total volume of 30 c.c. If concentrated solution is used this step is omitted. It is then heated at 56° C. for half an hour, when it is ready for injection.

421. Lines 4-5 *read*:

are: estimation of pressure, cell count, globulin reaction, Wassermann reaction, **and gold reaction**. The determination of pressure has already been described

422. Line 21 *add* after "article (21)":

The simplest method for the estimation of a protein increase is the Pandy test, which is performed as follows: The reagent consists of a saturated aqueous solution of carboic acid. To 1 c.c. of this reagent 1 drop of spinal fluid is added. The immediate formation of a bluish-white ring or cloud is the evidence of an abnormal protein content.

Line 24 *add* after "subject.":

LANGE GOLD REACTION.—This test must be carried out in a well-equipped laboratory. From $\frac{1}{2}$ to 1 c.c. of fluid should be collected in a separate clean tube. It is very essential that no blood or serum be in the fluid to be tested, and it is well to collect the last part of the fluid for the test so that the needle will be well washed.

423. *Add* under "References.":

Byrnes. Jour. A. M. A., 1914, LXIII, 2182.

Fordyce, J. A. Jour. A. M. A., 1914, LXIII, 552.

Gennerich. Münch. med. Wehnschr., 1915, LXII, 1696.

Ogilvie, H. S. Jour. A. M. A., 1914, LXIII, 1936.

Pandy. Neurol. Centralbl., 1910, XXIX, 915.

424. Reference 21 *read*:

21. Lange, C. Zeitsch. f. Chemotherap., 1912, I, 44.—**For full discussion of Gold Reaction see Miller, Brush, Hammer and Felton. Johns Hopkins Hosp. Bull., 1915, XXVII, 391.**

CHAPTER XV

PATHOGENIC FUNGI—SPOROTRICHOSIS, OÏDIOMYCOSIS, INCLUDING BLASTOMYCOSIS, AND ACTINOMYCOSIS

T. R. BROWN

436. Line 2 *add* after "Editors.":

MADURA FOOT

This disease is quite common in India and in various parts of the tropics; it has also been observed in Algiers and in America.

Madura foot, or mycetoma, resembles very closely actinomycosis in the general character of the lesions and the arrangement of the parasite in the form of colonies or granules. There seems to be but little doubt that these two conditions are distinct and that there are two varieties of Madura disease caused by different organisms. This disease usually assumes an extremely chronic character. The local disease is incurable except by operation. The organism causing this disease never develops secondary lesions in the internal organs. The most frequent part affected is the foot: hence the disease is spoken of as "Madura foot." In the affected part is noted a slow growth of granulation tissue, having an irregularly nodular character. In the center of these nodules there occurs a purulent softening, which is often followed by the formation of fistulous openings and ulcers. There is usually considerable enlargement and distortion of the part, frequently followed by necrosis of the bones. It is not unusual to find within the softened cavities and also in the spaces between the fibrous tissue small round bodies or granules resembling actinomycetes. These granules are yellowish or pinkish in color, resembling fish roe. The black granules are similar to gunpowder, and may by their conglomeration form nodules of considerable size. Owing to these two kinds of granules this disease has been divided into two varieties, which are known as the pale and black varieties. In both instances the granules are larger in size than in actinomycosis.

Morphology.—Morphologically this organism closely resembles ac-

tinomyces, but it possesses certain differences in cultural characters. It does not liquefy gelatin, but forms raised yellowish colonies, having umbilication of the center. On agar the growth is reddish in color. The organism grows well in the various vegetable infusions in which the actinomyces does not grow. This organism grows only under aërobic conditions. Experimental inoculation of various animals has failed to reproduce the disease. There is no doubt that the black variety, or streptothrix maduræ, and the actinomyces are distinct species.

PALE VARIETY.—When these roc-like granules are examined under the microscope they appear like actinomyces, showing an abundant mass of branching filaments with mycelial arrangement. The periphery of these masses sometimes shows club-like masses. These masses frequently are elongated and wedge-shaped, forming an outer zone to the colony which are connected by filaments.

BLACK VARIETY.—There has been considerable discussion in regard to the relation of this variety of the disease and the pale variety. Kanthack believed that the organism was the same in both varieties, and occurred in the black variety only in a degenerated form. Boyce and Surveyor, on the other hand, have pointed out differences, showing that the black variety is more highly organized, and that the branching filaments are thicker, hence they believe that it belongs to the hyphomycetes. J. H. Wright's observations confirm this view. The pigment may be dissolved by treating the granules with hypochlorite of sodium solution. The granules are then crushed between cover-glasses and examined. The black granules are composed of a homogeneous substance impregnated with pigment; in this substance there are mycelium with thick filaments or hyphæ and swollen segments, forming a zone with radiate arrangement. In the older granules the organisms are largely degenerated and present an amorphous appearance. Wright transferred a number of these black granules into various culture media, and was partially successful in growing the hyphomycete. The organism grows well on the ordinary culture media; on agar it forms a felted grayish mass; in old cultures the black granules appear with the mycelium. Microscopically, the organism appears as a mycelium having thick branching filaments with delicate transverse septa. In the older threads the segments are swollen, forming a string of oval-shaped bodies. So far as is known no spores are formed. Animal inoculations using cultures or the black granules from tissues have thus far been unsuccessful. Vincent found that iodid of potassium, which has a high value as a therapeutic agent in many cases of actinomycosis, has no effect in the case of Madura diseases.

Add under "References":

Boyce and Surveyor. Proc. Roy. Soc., London, 1893.

Kanthack, A. A. Jour. Path. and Bacteriology, I, p. 140.

- Page, Frothingham, and Paige. Jour. Med. Res., 1910, XXIII, 137-150.
- Vincent. Ann. de l'inst. Pasteur, VIII, 129.
- Wright, J. H. Jour. Exper. Med., III, 421.

CHAPTER XVI

SPECIFIC PROPHYLAXIS AND THERAPY IN DIPHTHERIA

G. H. WEAVER

453. Line 11 *add* after "bodies.":

Kaolin has the faculty of mechanically removing bacilli from the surfaces of mucous membranes and has been used locally with success by Hektorn and Rappaport. Careful examination of persistent carriers often discloses local conditions which favor the retention of the bacilli, such as enlarged tonsils and adenoids, and sinusitis. The removal of such tonsils and adenoids and the employment of measures to secure free drainage of the accessory sinuses are often followed by prompt disappearance of the bacilli.

CHAPTER XVII

TETANUS

WILLIAM H. PARK

459. Line 43 *add* after "**Symptoms.**":

There is, however, apparently an interval of time in which the toxin is in contact with the cells' surface, or is free in the cells' fluid, before true union takes place. According to experiments by Kraus, part of this toxin will pass out of the cells if they are surrounded by an antitoxic fluid, just as salts pass through a membrane into salt-free fluids.

466. Line 16 *read*:

ous, intravenous, **intraneural**, and intraspinal injections. The results with intraspinal

Line 19 *read*:

injections. **The intraneural injections had no appreciable effect.** The units required by the intraspinal method were less than

467. Line 6 *read*:

by us have been surprisingly good. The recoveries **in the cases treated by intraspinal injections** have been over 70

469. Lines 31-32 *substitute*:

During the past two years intraspinal injections have been given in nearly every case occurring in New York City. Dr. Nicoll and I collected the first twenty cases. The results showed 80 per cent. of recoveries.

In judging the effect of antitoxin given intraspinally in this series of cases, it must be remembered that the patients were not selected, but that every case of tetanus reported was given the benefit of the treatment regardless of the clinical condition. The series, therefore, may be said to be fairly representative of the type of the disease occurring in and about the city of New York. A few of these patients would undoubtedly have recovered if the intraspinal injection of antitoxin had not been given or, indeed, without any treatment other than symptomatic. The results obtained, however, in the saving of life are so much more favorable than

those in previous years, when large doses of antitoxin were recommended to be given by the intravenous and subcutaneous methods, that there can be no reasonable doubt that the low death rate, 20 per cent., here obtained was largely due to intraspinal dosage.

470. Line 4 *read*:

to 2,000 units, according to its size. In an adult 3,000 to 5,000 units should be

Line 44 to **471.** Line 1 *read*:

a week. The intraspinal injections had better be repeated after 24 and 48 hours. The antitoxin rapidly passes from the spinal fluid to the blood and it is possible that some toxin may enter the cord from the nerve trunks. The repeated injections certainly do no harm and seem to do good. The important thing is to give enough at the first pos-

471. Line 8 *read*:

sible a later intraspinal injection can be given. This, however, is of far less value than the intraspinal injection. Actual histories of a few cases with both the antitoxic and general treatment are given in Vol. II, page 351, also pages 273-274 of this supplementary volume. The amount should be

CHAPTER XVIII

PNEUMOCOCCUS INFECTION

RUFUS I. COLE AND A. R. DOCHEZ

474. Line 12 *add* after "susceptibility.":

Dochez and Avery have recently shown that pneumococci belonging to what are known as Groups I and II do not occur in the mouth secretions of healthy persons unless such individuals have been in intimate contact with cases of pneumonia in which infection was due to these types of pneumococci. Such an observation indicates that infection with these varieties of pneumococcus spreads either through contact with an infected individual or through association with a healthy carrier.

485. Line 16 *read*:

infections, particularly lobar pneumonia, for the past **six** years. The

486. Line 29 *read*:

ferent organisms. In **300** cases of pneumonia studied, the number of cases
Substitute for "Table I":

Classification of Three Hundred Cases of Pneumonia

Type of Organism	Number of Cases	Percentage
1	102	34
2	99	33
3 (Mucosus)	36	12
4 (Heterogeneous)	63	21

487. Lines 6-8 *read*:

less efficacious, against organisms of Type II. **The immune serum produced against organisms of Type III is of somewhat lower potency than that against Type II, and for this reason it has not seemed likely that it is of sufficient value for therapeutic use in man.** It is manifestly impossible to utilize a specific serum in infec-

Substitute for "Table II":

Mortality

Cases Due to	Number of Patients	Died	Percentage
Type I.....	30	10	33.33
Type II.....	30	10	33.33
Type III.....	15	7	46.66
Type IV.....	25	3	12.00
Total.....	100	30	30.00

488. Lines 11-18 *substitute*:

Serum prepared and tested for specificity in this manner has now been used by the authors in a considerable number of cases of pneumonia. Treatment has been limited to injections with antipneumococcus serum Types I and II. Treatment of pneumonia with serum Type I has given very good results. In sixty-five cases so treated the mortality has been 7.5 per cent., which represents a considerable reduction in the mortality observed in untreated instances of infection with this type of organism. These statistics include one individual who was moribund at the time of the first treatment, and another who died from pulmonary embolism after recovery from the pneumonia. The use of serum Type II seems to be much less effective as a therapeutic measure. The reduction in mortality of treated cases of this type as compared with the untreated has been so small that we have discontinued the use of the whole serum and attempts are now being made by Chickering to increase the potency of this serum by the use of special methods of concentration.

Lines 26-28 read:

serum. The early determination of the type of organism is of great importance, since the earlier in the disease that serum treatment is inaugurated the greater are the chances of a favorable result.

489. Lines 11-15 *read*:

in cases of pneumonia treated with immune serum. A number of patients treated with Type 1 serum have developed empyema following their pneumonia. All of these have recovered after the usual surgical procedures with the exception of one individual who died from a secondary streptococcus septicemia. In a small number of instances fluid has developed in the chests of serum-treated patients which on removal has been found to be relatively clear and on culture to be free from microorganisms.

Line 20 *add* after "commenced.":

In all cases the occurrence of pneumococcus in the blood has been carefully studied. Whenever a bacteremia has existed, the organisms with but one or two exceptions have disappeared from the blood after a single injection of serum, that is to say within an interval of from eight to twelve

hours. In general, therefore, one large dose of serum seems sufficient to sterilize the blood, and the conclusion seems justifiable that if organisms are not present in the blood, the administration of serum will prevent their entrance.

490. Line 39 *add* after "encountered.":

Further development in the methods of treating this latter variety of pneumonia is anticipated, and should the endeavors being carried on at the present time prove successful, it would then be possible to treat effectively with specific antisera about seventy per cent. of all cases of lobar pneumonia.

501. Line 38 *add* after "serum.":

Moore in this country has carried on an extensive investigation of the action of ethylhydrocuprein or optochin, as it is more commonly called, against the pneumococcus. He has tested the bactericidal action of the drug *in vitro* against the different biological groups of pneumococcus and finds that it is equally active against all types, but that it possesses no such specific action against streptococcus. This investigator has also found that the blood of rabbits after the administration of optochin, acquires bactericidal powers for pneumococcus. The best results are obtained by subcutaneous injection. It is somewhat less active in rabbits when given intramuscularly, and seems to exert no activity when administered by mouth. In order to obtain satisfactory effects by the intravenous route, it was necessary to give the drug in toxic amounts. Moore has also found that the blood serum of man becomes bactericidal for pneumococcus after the administration of 0.5 gram of optochin by mouth or subcutaneously. When given subcutaneously, the drug is very irritating and may produce necrosis with the formation of a sluggish ulcer. He has also tested the value of combining optochin with specific antipneumococcus serum in the treatment of pneumococcus infection in animals, and finds that doses of optochin, which in themselves are so small as to have no therapeutic value, enhance many times the protective value of threshold doses of antipneumococcus serum.

503. Line 6 *add* after "administration.":

The occurrence of the European war has delayed any increase in the general experience of the value of optochin as a method for treating lobar pneumonia. However, the drug has been rather widely used in Germany and a summary of the results obtained has recently been published by Leschke. The cases are divided into two groups,—those treated before the third day of the disease and those treated after the third day. In the two hundred and four cases treated before the third day, the mortality was 5 per cent., and in the one hundred and nineteen cases treated after the third day, was 20 per cent. The mortality for the total three

hundred and twenty-three cases was 1.1 per cent., which represents a considerable reduction in mortality from that ordinarily observed. Moore and Chesney have recently made a very careful study of the effect of optochin in lobar pneumonia, and also give a summary of the total number of treated cases up to the present time. In order to obtain an accurate knowledge of the use and effect of the drug, recourse should be had to the original article. These investigators recommend a dosage of the drug, based on body weight, of from 0.024 to 0.026 gram per kilogram, which is the amount necessary to insure bactericidal development by the blood serum of the individual under treatment. An initial dose of 0.45 gram is given and the remainder divided into small doses of 0.15 gram given at from two to three hour intervals. The advantage of this method is that the bactericidal power of the blood rises rapidly and is maintained at a fairly constant level throughout the course of treatment. The administration of the drug is continued for about twenty-four hours after the temperature has fallen.

Optochin in certain individuals gives rise to toxic symptoms which constitute a distinct disadvantage in its use. The margin of safety is rather narrow and great care must be taken to avoid too large doses. The toxic effects seem to depend somewhat upon too great a concentration of the drug in the blood at one time and this is the reason for the repeated small doses, since when 0.5 gram doses are given the concentration rises rapidly and generally falls considerably before the time for the next dose. Optochin, like quinin, exhibits its chief toxic action against the special senses. Deafness not infrequently occurs during treatment, but recovery seems to be complete, and this is not necessarily regarded as an indication for the cessation of treatment. The effect of optochin on the eye, when given in toxic doses, is much more serious, and the administration of the drug should not be continued after the appearance of eye symptoms. These consist of widening of the pupil with failure to react to light, dimness of vision, and in some instances complete blindness. In extreme cases the eye grounds show pallor of the retina with marked narrowing of the vessels. Complete blindness may persist for a week or more, with gradual return of vision. In many instances recovery is complete, but in some there is apparently permanent damage to the retina so that although central vision is normal, there is marked contraction of the visual fields. In only one instance so far reported has blindness been permanent, a case in which a very large dosage of the drug was employed. Toxic eye symptoms, however, may develop after a comparatively small total dosage, 2.0 grams in 0.5 gram doses in one instance. Although such toxic effects are a serious disadvantage, there is reason to believe that by careful methods of administration they may be avoided or greatly minimized, and, in view of the gravity of pneumonia as a disease, it is to be expected that optochin will receive a wide application.

505. Line 36 *add* after "latter.":

Since the introduction by Morgenroth of optochin into the therapy of pneumococcus infections, this drug has been used extensively in Germany in the treatment of *ulcus serpens*. Most of the investigators report satisfactory results from its application. A 1 to 2 per cent. water solution of the drug is applied locally and is said to result in unusually rapid healing of the ulcer. It causes no damage to the corneal epithelium in this dilution, and the burning sensation caused by its application can be obviated by the use of a local anesthetic. *Pneumococcus* ulcer of the cornea usually results in considerable destruction of tissue with scar formation. Treatment with optochin is said to give a more satisfactory end result as far as permanent damage to the cornea is concerned than any of the methods hitherto employed, especially those in which the cautery is used.

[Ophthalmologists in this country report distinctly favorable results from the treatment of *pneumococcus* ulcer of the cornea by local applications of optochin.—Editors.]

Add under "References.":

Dochez and Avery. *Jour. Exp. Med.*, 1915, XXII, 105.

Moore. *Jour. Exp. Med.*, 1915, XXII, 269.

Leschke. *Deutsch. med. Woch.*, 1915, XLI, 1359.

Moore and Chesney. *Personal Communications*. Original article soon to appear.

CHAPTER XIX

THE ETIOLOGY AND SPECIFIC TREATMENT OF RHEUMATISM

E. C. ROSENOW

513. Line 18 *add* after "dogs.":

[The acquirement of new characters by organisms seems to be an occasional occurrence, but a frequent change in morphologic characteristics does not seem to be in keeping with other facts of biology or bacteriology. When organisms do undergo changes these changes are perhaps more likely to concern physiologic characters, such as the fermentative reactions, than they are to involve changes of morphology. The conditions required by experimentation along this line are exacting, and one must be extremely cautious in the interpretation of results which seem to indicate sudden accession or loss of biological characteristics.—Editors.]

CHAPTER XX

EPIDEMIC CEREBROSPINAL MENINGITIS

A. SOPHIAN

548. Line 4 *add* after "irrigation.":

Haynes has conceived the idea of treating certain hydrocephalic conditions by draining the fluid from the hydrocephalic cavity into one of the easily accessible sinuses, attempting to reproduce the course of the fluid into the blood stream. The operation termed by him cisterna, sinus drainage, seems to be based on careful experimental and clinical observation and is worth trying in cases of posterior basic meningitis, where the more simple methods do not give immediate encouragement.

549. Line 35 *add* after "treatment.":

Child 11 months old was seen by the writer in consultation with Dr. Saulsberry. There was a history of three weeks' illness conforming in every respect to epidemic meningitis. First lumbar puncture yielded a very large quantity of turbid fluid showing a few meningococci. The usual serum treatment was immediately instituted. Puncture and serum injection were repeated twice. There was very marked clinical improvement, but still evidence of a pronounced hydrocephalus and a few meningococci could still be found when the parents decided that the child was very much better and opposed further treatment. The writer did not see the child again until 2 weeks later, when Dr. Saulsberry reported that the child was having severe convulsions and he thought was about to die. The child at this time presented a typical picture: a peculiar facies, the eyes open, staring with lids retracted; the face blank and expressionless, disturbed at times by a grimace accompanied by a shrill hydrocephalic cry. The head was markedly extended and the body showed extreme form of opisthotonos, the head almost touching the buttock. The child did not seem to see and could not swallow. The head was markedly enlarged, the sutures widely separated, anterior fontanelle markedly bulging; the head felt like a bag full of water. There were marked rigidity of the whole body and persistent convulsive spasm of the upper extremi-

ties, which were extended with hands clenched and lower extremities with the feet extended and toes flexed. There was a marked *tâche cérébrale*. Heart action was rapid and intermittent, but at times during the day it was slow and intermittent. Respirations were slow, irregular, with long periods of apnea, breathing corresponding best to the Biot type. Reflexes were markedly exaggerated. The child had been lying in this "hypnotic state" for several days. Occasionally there was explosive vomiting.

The child presented evidence of terrific hydrocephalus; the peculiar facies, the staring eyes, the retracted lids, the extreme opisthotonos suggested that we were dealing with posterior basic meningitis.

Lumbar puncture made at two levels yielded a few drops of cerebrospinal fluid. A ventricular puncture was then done.

The right ventricle was first tapped, 50 c.c. of slightly turbid cerebrospinal fluid was removed under very high pressure and 20 c.c. of serum containing 2.10 per cent. of tricrosol preservative was injected. There was a fall of 10 mm. of mercury in blood pressure on the removal of the fluid, but no change on injecting the serum. The next day the condition was somewhat improved, convulsions were controlled, but other pressure signs were again present. The left ventricle was tapped and 80 c.c. of slightly turbid cerebrospinal fluid was again removed and 20 c.c. of serum injected with blood pressure change as on the previous day. The cerebrospinal fluid obtained the first day showed a moderate number of pus cells and a few meningococci, extra- and intracellular. The second fluid showed only intracellular meningococci.

Two days later the right ventricle was again tapped; 60 c.c. of clear fluid was removed. No meningococci were found. The child showed considerable improvement though he still did not seem to see, opisthotonos less marked, pulse and respiration were less irregular. The child nursed, had no temperature, cried more normally and in general was much improved.

The parents again decided against further treatment. The child continued to improve, and two weeks after the last puncture all the pressure signs and opisthotonos had disappeared, the child could see; nutrition was improved.

I did not see the child until two months later, when Dr. Saulsberry called me on account of attacks of dyspnea and cyanosis with loss of consciousness, which first appeared one month previously, coming on at intervals of a few days but in the past week several times daily.

The child presented a most astonishing picture. He was bright, stout, and had grown tremendously. In two months he had put on the growth that usually requires a year and a half. He was active, playful, could see well, and had developed mentally almost in proportion to his skeletal growth. The head was large and showed signs of hydrocephalus. There

was also evidence of a large thymus. I interpreted the condition as due to a persistent hydrocephalus and attributed the excessive skeletal development to a possible pituitary involvement. Lumbar puncture was performed and 60 c.c. of clear fluid removed. *The puncture proved that the communication between the ventricles and subarachnoid space had been reëstablished.* The child did not have convulsions until three days later. For the next two weeks convulsions occurred once every few days, and seemed to be generally improved after the puncture.

The last the writer heard of the child, six weeks later, the convulsions were less frequent and there was continued good development.

This case is of importance as demonstrating the value of therapy. The recovery was complete with the exception of subsequent convulsive seizures. The complicating hyperpituitarism and thymic growth were of unusual interest. It also shows that communication between ventricles and subarachnoid space can be reëstablished. This may be explained when the closure is due to an inflammatory exudate.

578. Add under "References.":

Haynes. New York State Jour. of Med., April, 1916.

CHAPTER XXI

GONOCOCCAL INFECTIONS

ERNEST E. IRONS

596. Line 25 *add* after "evaporation.":

A further explanation of the superiority of closely stoppered tubes over those more loosely plugged with cotton for cultivation of the gonococcus is afforded by the studies of Wherry and Oliver. They found that in cultures made by inoculating pus-containing gonococci, very few colonies appeared on the tubes or plates kept under aerobic conditions, whereas many colonies grew in the cultures placed under conditions of partial oxygen tension. The gonococcus therefore appears to be a *micro-aërophile*, or partial tension organism. Wherry and Oliver employed a modification of the method of Nowak for producing conditions of partial oxygen tension, attaching by rubber tubing, to the tube inoculated with the gonococcus, a tube freshly inoculated with *B. subtilis*.

616. Line 26 *add* after "vaccines.":

Block saw improvement in gonococcal arthritis following the injection of typhoid vaccine as well as following gonococcal vaccine, and suggests that the improvement may be due to nonspecific effects of the reaction on gonococcus infection.

618. Line 7 *read*:

reactions, including the reaction of complement-fixation, **together with the absence of other forms of focal infection** will furnish

Line 8 *add* after "diagnosis.":

It must always be remembered that iritis from other sources of infection may occur as well in a patient who is suffering from gonorrhea as in other patients.

Line 11 *add* after "immunization.":

Local treatment of the primary disease in urethra and prostate must not be neglected.

621. *Add* under "References.":

Block. Cor.-Bl. f. schweitz. Aerzte, 1914, XLIV, No. 44.
Wherry and Oliver. Jour. Inf. Dis., 1916, XIX, 288.

CHAPTER XXII

VACCINE THERAPY IN DERMATOLOGY WITH SPECIAL REFERENCE TO ACNE AND FURUNCULOSIS

J. FRANK WAUGH

630. Line 8 *add* after "cines.":

Fox reports two cases treated with autogenous vaccine that developed alarming symptoms: Following the first injection there were high fever, headache, nausea, dizziness and severe local symptoms. Similar cases have been reported by Wallace and Hitchins.

633. Line 23 *add* after "day.":

Fox recently reported one hundred cases of acne and furunculosis treated with vaccines. The acne cases were classified in two groups, those having "coarse" and more deeply seated lesions being placed in the first group. The second group comprised those with "fine" or more superficial papules and pustules. Both autogenous and stock preparations of vaccine were used; the dosage is not given. Three months after treatment with autogenous vaccines, no patient was free from lesions; 25 per cent. of the cases showed improvement. With stock vaccines, 18 per cent. showed improvement three months after the last treatment. During the course of the treatment a much larger percentage showed improvement.

In the furunculosis cases the percentage of cured and improved was the same, in those treated locally and in those treated both locally and with vaccines.

635. Lines 16-17 *read*:

Vaccines have been tried in other dermatoses of **both known and** unknown origin, such as the different types of pemphigus, mycosis fungoides, **favus and ringworm**, dermatitis her-

Add under "References.":

Fox. J. A. M. A., 1916, LXVI, 2064.

Wallace. J. A. M. A., 1914, LXII, 1166.

Hitchins. Interstate Med. Jour., 1914, XXI, 537.

CHAPTER XXIII

INFECTIONS OF THE MOUTH

ERNEST E. IRONS

639. Lines 10-18 *substitute*:

Pyorrhea and Alveolar Abscess.—The treatment of pyorrhea by the injection of vaccines is justified neither by anatomic and pathologic considerations nor by clinical results. Alveolar abscess calls for surgical treatment, and when this is afforded either by extraction or by other approved dental procedure, the lesion heals without the use of vaccines.

641. Line 12 *add* after "rapid.":

In general it may be stated that the vaccines have added little, if anything, of proved value in the treatment of infections of the ear and sinuses. Such lesions call for appropriate surgical or other treatment which shall secure adequate drainage and the removal of sources of mechanical irritation.

CHAPTER XXVII

ANTIANTHRAX SERUM

ERNEST E. IRONS

Antianthrax serum has proved of value in the protection of animals against anthrax, and also in the cure of the disease. The serum has also been used in combination with injections of bacillary or spore vaccine in the prophylactic immunization of animals. The mode of action of the serum is not well understood, but the results obtained with it in animals justify its employment in anthrax infections in man.

Sera having a protective power against artificial anthrax infections are obtained by the immunization of sheep, horses, and cattle. In the treatment of anthrax in animals, the administration of serum is followed by a drop in temperature and decrease in severity of symptoms. A relapse may occur on the second or third day, and calls for further injections of serum. It has been proved that animals affected with anthrax may recover after an injection of potent serum, even after the bacilli are found in the blood (Eichhorn).

Sclavo reports a mortality of 6.09 per cent. in 164 cases of anthrax in man treated with serum, as against a mortality of 24.16 per cent. in cases which received no serum. Other clinicians of experience in this disease in Germany testify to the value of serum (Sobernheim). The report of the Bradford Investigation Board in England (1912) favors the use of Sclavo's serum as a valuable remedy, and refers to four severe cases in which serum was used with recovery.

The serum should be given in doses of 20 to 40 c.c., subcutaneously, or in severe cases intravenously. In desperate cases larger doses have been given with apparent benefit (Sobernheim).

The treatment of malignant pustule is primarily surgical, but, where available, serum should be given as well, particularly in view of the evidence of its prophylactic value in animals.

Kolmer recommends the following method of treatment: "If the lesion is relatively small with little or no evidence of toxemia, a blood

culture should be made by placing 2 to 5 c.c. of blood in a flask of neutral bouillon. An intravenous or intramuscular injection of 20 to 50 c.c. of serum is given. The object is to introduce serum before the lesion is handled, and the blood culture is the best indication for subsequent injections of serum and serves as a guide to prognosis." The lesion should be excised with as little handling as possible, and the site dusted with calomel. In case the edema does not subside and infection is spreading at the edges of the wound further excision of tissue may be necessary, and more serum should be injected. The injection of phenol into the wound has been recommended. If after 24 hours the cultures show anthrax bacilli, 100 to 200 c.c. of serum are to be injected intravenously. Daily blood cultures are made, and serum injected until the blood becomes sterile. Kolmer states that in his experience patients with sterile blood cultures have invariably recovered, and those with bacilleemia have usually died.

REFERENCES

- Eichhorn, A. Bull. 340, U. S. Dept. Agri.
Kolmer. Infection, Immunity, and Specific Therapy, 1915, 767.

CHAPTER XXIX

ROCKY MOUNTAIN SPOTTED FEVER

ERNEST E. IRONS

660. Line 21 *add* after "observers.":

At present the most promising means of combating the disease appear to be those of prophylaxis, directed against the wood tick, by the bite of which the disease is transmitted to man.

CHAPTER XXXI

HODGKIN'S DISEASE

ERNEST E. IRONS

665. Line 21 *add* after "*maligni*.":

Bunting and Yates also isolated a diphtheroid organism from the granulomatous masses of Hodgkin's disease and studied the lesions in monkeys produced by the inoculation of cultures of the organism.

669. Line 34 *read*:

Hodgkin's disease and in cases clinically **and histologically** lymphosarcoma, and the occur-

Lines 36-37 *read*:

kin's disease, suggest that **all these bacteria may be merely secondary invaders which have been filtered out from the blood.** The more carefully the bacteriology

Line 41 *add* after "*unsuspected*.":

The bacteriologic findings in Hodgkin's disease have stimulated the search for diphtheroids in other tissues, normal and pathologic, unassociated with Hodgkin's disease, with the result that these bacteria have been found to be widely distributed in the body. While it is possible that the febrile periods noted so frequently in Hodgkin's disease may be due to the activity of these secondary invaders, the evidence at hand seems to indicate that we must look elsewhere for the primary etiologic agent of Hodgkin's disease.

J. J. Moore was unable to obtain complement-fixation with the serum of persons suffering from Hodgkin's disease, using antigens prepared from the diphtheroid bacilli, although he did obtain such reactions in horses, monkeys and rabbits, following immunization with the bacilli.

After an extensive study of fifty cases of Hodgkin's disease, in which the patients were treated with vaccines either alone or in combination with Roentgen rays and arsenic, Billings was able to observe no permanent benefit from vaccines prepared from the organisms isolated. In those

cases in which improvement followed, relapse occurred later, so that the temporary initial improvement seemed attributable to spontaneous regressions, or to the effects of the Roentgen rays and arsenic, rather than to vaccines.

670. *Add* under "References.":

Moore, J. J. Jour. Infec. Dis., 1916, XVIII, 569.

CHAPTER XXXIII

HYDROPHOBIA

ANNA WESSELS WILLIAMS

713. Line 10 *read*:

that they pass chiefly, if not exclusively, along the nerve fibers, **probably in the surrounding lymph spaces**, to the

715. Line 20 *read*:

growth of the organism outside of the body. **The larger bodies described by Negri are no doubt nonspecific crystalline substances. They have been found by us in tuberculous sputum as well as in ascitic fluid. Noguchi's work has not yet been**

716. Line 16 *read*:

linger) that **rabies** virus, under certain conditions of dilution and suc-

719. Line 33 *read*:

tically; some do not bark **more than usual**. The majority do not have **fear of water**. They

731. Lines 27 to 732. Line 1 *read*:

to 1914 inclusive they treated **5,134** cases infected by rabid animals, with a total mortality of **0.46** per cent. and a corrected mortality of **0.18** per cent. They have had 7 cases of definite paralysis with two deaths. **About nine thousand** cases in all, including those not bitten

732. Line 10 *add* after "bites.":

The following table shows the modifications of New York City Health Dept. (Fielder). It will be seen that Scheme 2 is somewhat stronger than Scheme 1, since it contains three more injections of two-day cord, and much stronger than Scheme 3, which includes nothing more active than three-day cords. Scheme 2 is very similar to the one employed by the Hygienic Laboratory of the U. S. Public Health Service, Washington, D. C., and by most of those who produce antirabic vaccine in this country, with the following differences: 1. The amount of cord per dose was only two-thirds as much as that employed in the Washington scheme. 2. We used a two-day cord instead of one-day cord on the eighth and twenty-first days.

Cord Dried	Scheme 1	Scheme 2	Scheme 3
	Jan. 1, 1912, to Aug. 2, 1913	Aug. 3, 1913, to May 6, 1914	May 7, 1914, to Mar. 7, 1916
	Number of Injections in 21 Days	Number of Injections in 21 Days	Number of Injections in 21 Days
Ten days.....	3	0	0
Nine days.....	3	0	0
Eight days.....	1	1	2
Seven days.....	1	1	2
Six days.....	1	1	2
Five days.....	1	2	2
Four days.....	5	5	9
Three days.....	5	7	8
Two days.....	5	8	0
Number of patients treated.....	1,408	811	911
Cases of paralysis....	1	6 (one fatal)	0
Cases of rabies.....	4	2	4

734. Line 23 *read*:

efficiency of this method in human beings. As far as animal experiments show this method, according to Poor, promises well.

736. Line 13 *add* after "complications.":

Poor, experimenting on animals with this method, reports results comparing favorably with those of the Harris method.

742. Table *read*:

Year	Cases Treated	Number of Deaths	Percentage
1886.....	2,671	25	0.94
1887.....	2,770	14	0.79
1888.....	1,622	9	0.55
1889.....	1,830	7	0.38
1890.....	1,540	5	0.32
1891.....	1,559	4	0.25
1892.....	1,790	4	0.22
1893.....	1,648	6	0.36
1894.....	1,387	7	0.50
1895.....	1,520	5	0.38
1896.....	1,308	4	0.30
1897.....	1,529	6	0.39
1898.....	1,465	3	0.20
1899.....	1,614	4	0.25
1900.....	1,420	4	0.28
1901.....	1,321	5	0.38
1902.....	1,005	2	0.18
1903.....	628	2	0.32
1904.....	755	3	0.39
1905.....	721	3	0.41
1906.....	772	1	0.43
1907.....	786	3	0.38
1908.....	524	1	0.19

Year	Cases Treated	Number of Deaths	Percentage
1909.....	467	1	0.21
1910.....	401	0	0.00
1911.....	341	1	0.29
1912.....	395	0	0.00
1913.....	330	0	0.00
1914.....	373	0	0.00
Total.....	34,492	129	0.35

747. *Add* under "References.":

Fielder, F. S. Paralysis Complications, Pasteur Antirabic Treatment, Col. Stud. Bur. Lab., New York City Health Dept., 1914-15, VIII, 239.

Jelinek and Gibson. Experiments on the Comparative Antirabic Immunity Produced by the Pasteur Virus, the Harris Desiccated Virus and the Cumming Dialyzed Virus, Col. Stud. Bur. Lab., New York City Health Dept., 1914-15, VIII, 113.

Poor, D. W., and Jelinek. Experiments on the Comparative Antirabic Immunity Produced by the Pasteur Virus, the Harris Desiccated Virus and the Cumming Dialyzed Virus, Col. Stud. Bur. Lab., New York City Health Dept., 1914-15, VIII, 113.

GENERAL INDEX

GENERAL INDEX

(B.F.) refers to Billings-Forchheimer's "Therapeusis of Internal Diseases."

(F.) refers to Forchheimer's "Therapeusis of Internal Diseases."

(Sup.) refers to Supplementary Volume.

Where no key is given the material appears in the Forchheimer and Billings-Forchheimer volumes.

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